"A Prospective Observational Study to Evaluate the Biochemical Response of Radical Local Therapies in Patients with Locally Advanced and Oligometastatic Carcinoma Prostate"

Thesis submitted to

The faculty of

All India Institute of Medical Sciences, Bhopal

For the award of the degree of M.Ch in the subject of

Urology

By

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TABLE OF CONTENTS

Serial No.	Content	Page No.
1.	List of Tables	xiii
2.	List of Figures	xiv
3.	List of Abbreviations	xvi
4.	Introduction	18
5.	Review of literature	20
6.	Aims and objectives	44
7.	Materials and methods	45
8.	Results	57
9.	Discussion	119
10.	Limitations and future prospects	125
11.	Conclusion	125
12.	References	127
13.	Study Proforma- Appendix 1	149
14.	Participant Information Sheet – English- Appendix 2	151
15.	Participant Information Sheet – Hindi- Appendix 3	157
16.	Participant Informed Consent Form- Appendix 4	162
17.	Master Chart- Appendix 5	

LIST OF TABLES

Table no.	Title	Page no.
1	Clinical TNM Classification of PCa	24
2	ISUP System	26
3	EAU Risk Stratification For BCR of Localised and Locally Advanced PCa	26
4	Criteria for Defining OMPCa	33
5	Comparative Table of RCTs: STAMPEDE, GETUG-AFU 15, CHAARTED	37
6	Comparison of HORRAD and STAMPEDE Trial	42
7	Summary of All Descriptive Parameters	71-72
8	Relative Risk (RLT and Preoperative N Stage)	93
9	Summary Table for Association between RLT and Parameters	95-97
10	Relative Risk Table (ADT and Preoperative N stage)	114

LIST OF FIGURES

Figure	Title	Page no.
1	Prostate Biopsy Flowchart	29
2	Flowchart of EBRT in Locally Advanced and OMPCa	50
3	Bladder neck sparing approach	53
4	Distribution of Participants in terms of RLT	58
5a-5b	Distribution of Participants in terms of Age	60
6a-6c	Distribution of Participants in terms of Initial PSA (ng/mL)	62-63
7	Distribution of Participants in terms of PIRADS Score	64
8	Distribution of Participants in terms of ISUP	65
9	Distribution of participants in terms of clinical T Stage	66
10	Distribution of participants in terms of pathological T Stage	67
11	Distribution of Participants in terms of preoperative N Stage (Clinical)	68
12	Distribution of participants in terms of M Stage	69
13a-13b	Distribution of participants in terms of Number of Osseous Metastases	70-71
14a-14b	Association Between Type of RLT and Age (Years)	75-76
15	Association Between Type of RLT and PSA (ng/mL) (Initial)	78

16a-16b	Association Between Type of RLT and PSA (ng/mL) at 3 Months	80
17a-17b	Association between RLT and Change in PSA (ng/mL) at 3 Months	82
18a-18b	Association between RLT and PIRADS score	84-85
19a-19b	Association between RLT and ISUP	87
20a-20c	Association between RLT and Clinical T Stage	89-90
21a- 21c	Association between RLT and preoperative N stage (Clinical)	92-93
22	Association between RLT and M stage	95
23	Association between Initial PSA and Change in PSA at 3 Months	98
24	Association between Clinical T Stage and Change in PSA at 3 Months (ng/mL)	101
25a-25d	Association between Preoperative N Stage and Change in PSA at 3 Months (ng/mL)	103-104
26a-26b	Association between M stage and Change in PSA (ng/mL) at 3 Months	106
27	Association between Number of Metastases and Change in PSA (ng/mL) at 3 Months	107
28a-28b	Change in PSA over time (ng/mL)	110
29	Association between ADT and Clinical T Stage	112
30	Association between ADT and Preoperative N Stage (Clinical)	114
31	Association Between Margins and PSA (ng/mL) at 3 Months	116

LIST OF ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
ASR	Age standardised rates
BCR	Biochemical Recurrence
DRE	Digital Rectal Examination
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
ePLND	Extended Pelvic Lymph Node Dissection
ED	Erectile Dysfunction
GS	Gleason Score
Gy	Gray
IDC	Intraductal Carcinoma
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
ISUP	International Society of Urological Pathology
LAPC	Locally Advanced Prostate Cancer
LHRH	Luteinising Hormone Releasing Hormone
LUTS	Lower Urinary Tract Symptoms
MetS	Metabolic Syndrome
mHSPCa	Metastatic Hormone Sensitive Prostate Carcinoma
MRI	Magnetic Resonance Imaging
OMPca	Oligometastatic Prostate cancer
OR	Odds Ratio
PCa	Prostate Cancer
PSA	Prostate specific antigen
PSA-d	Prostate specific antigen density

PSMA PET	Prostate Specific Membrane Antigen Positron Emission Tomography
RLT	Radical Local Therapy
RP	Radical Prostatectomy
TNM	Tumor, Node, Metastases
UICC	Union for International Cancer Control
VMAT	Volumetric Modulated Arc Therapy

INTRODUCTION

Prostate cancer is one of the most common cancers among men all over the world[1], and its incidence is on the rise in the Indian subcontinent. In India, prostate cancer accounts for about 6.8% of all male cancers, with more than 35,000 new cases diagnosed annually[2]. This increase is attributed to lifestyle changes, growing life expectancy, and advancements in diagnostic methods such as PSA screening and modern imaging technologies[3]. In. contrast to Western countries, where prostate cancer is often detected in its initial stages, patients in India tend to present with more advanced stages of the disease, including locally advanced and metastatic prostate cancer, primarily due to limited awareness and lack patient education and healthcare access[3,4].

Locally advanced prostate cancer, where the tumour extends beyond the prostate but has not yet spread to distant sites, is a frequent presentation in the Indian population[4]. Around 50% of prostate cancer cases in India present with LAPC or OMPCa [4]. The median survival for patients with metastatic prostate cancer remains poor, typically ranging between 2 to 3 years, depending on the extent of metastasis, treatment response, age, performance status and access to care[5,6].

The treatment of locally advanced and OMPCa, where the metastatic burden is limited, is still a conundrum. OMPCa is characterised by a limited number of metastatic lesions, usually fewer than five without any visceral metastases [7]. Although systemic therapies have advanced, the role of radical local therapies, in managing these patients is still being probed, the role of EBRT is well established, however there is no unison on the role of radical prostatectomy in this subset of patients[8].

Radical prostatectomy, mainstay of treatment for localised prostate cancer, is also being considered for patients with locally advanced and OMPCa[7]. Till recently, systemic therapies such as androgen deprivation therapy (ADT) or chemotherapy have been the

linchpins for management of mHSPCa [8]. However, recent literature is significative of that aggressive local control of the primary tumour through RLT could benefit some patients and can potentially delay disease progression and metastatic spread[9-12].

The logical basis for offering RLT to patients with LAPC and OMPCa is based on the "seed and soil" hypothesis. This proposes that the primary tumour sustains and potentiates metastatic spread[13]. By targeting the primary tumour, the overall disease burden and the risk of further metastasis may be decreased. This also allows for better monitoring of disease progression through periodic checks of PSA levels, which are otherwise influenced by the presence of the primary tumour[14]. This is relevant in OMPCa, where the primary tumour may continue to drive systemic progression even with a limited number of metastatic lesions[15].

These discussions underscore the complexity of managing OMPCa, which occupies a middle ground between localised and widely metastatic disease. Prostate cancer's slow progression, combined with advancements in imaging techniques such as PSMA PET/CT, has enabled earlier detection of metastatic lesions, potentially opening up new opportunities for curative-intent treatments like radical prostatectomy[16]. However, further research is needed to find the patient subgroups that are most likely to benefit from surgery and to refine treatment protocols that maximise outcomes while minimising risks.

This prospective observational study aims to contribute to the growing body of evidence regarding the role of RLT in treating LAPC and OMPCa by evaluating the biochemical response to radical local therapies. Specifically, the study will assess PSA reductions at three-month intervals following radical prostatectomy or EBRT.

REVIEW OF LITERATURE

Epidemiology of Prostate Cancer

Prostate cancer (PCa) remains an immensely consequential health concern for men globally. As of 2020, approximately 1.4 million new cases were recorded, accompanied by 375,000 deaths, positioning it as the second most frequently diagnosed malignancy among men worldwide[17,18]. In Europe, it not only ranks as the most prevalent male cancer but also stands as the third leading cause of cancer-related mortality[19].

Autopsy findings demonstrate that the prevalence of PCa is 5% among men under the age of 30, with this figure escalating by an OR of 1.7 per decade, reaching an astonishing 59% in men over 79 years [20]. Further, this prevalence exhibits significant variability based on ethnic and geographic factors[21].

The incidence of clinically diagnosed PCa varies significantly across regions, mainly due to differences in PSA testing and impact of screening guidelines[22]. The highest incidence rates are observed in Australasia followed by North America, with ASRs of 111.6 and 97.2 per 100,000, respectively. Conversely, the incidence in Eastern and South-Central Asia is markedly lower[23]. Ethnicity plays an essential role in this variation, with populations of African descent experiencing notably higher mortality rates compared to other demographic groups[24].

Aetiology of Prostate Cancer

Familial History and Hereditary Factors: A family history of PCa is a well-established risk factor, reinforcing the notion of a genetic predisposition to the disease[25,26]. Men of African descent, particularly those in Western nations, often face poorer outcomes due to a confluence of biological, socioeconomic, and healthcare-related factors [27]and are likely to be diagnosed at advanced stages of the disease and experience higher rates of progression

post-treatment in comparison to Caucasian men[28,29]. Genetic studies have identified numerous variants that augment susceptibility to PCa, particularly among men of African ancestry [30]. However, true hereditary PCa—defined as three or more cases within a family, or diagnoses occurring prior to the age of 55—comprises a small fraction of overall cases [31].

Germline Mutations: GWAS have identified in excess of 100 common genetic loci associated with an elevated risk for PCa, especially, aggressive variants of the disease[32,33]. Among men diagnosed with metastatic PCa, a higher preponderance of germline mutations, has been observed[34]. Carriers of BRCA2 mutations, have an elevated risk of aggressive PCa, and worse clinical outcomes have been reported in those harbouring BRCA1/2 mutations[35,36].

Environmental and Lifestyle Risk Factors: A variety of environmental and lifestyle factors have been implicated in the risk of PCa. Notably, Asian immigrants to the U.S. display approximately half the risk of developing PCa compared to U.S.-born individuals of Asian descent, underscoring the impact of environmental and dietary factors[37].

Metabolic Syndrome: Individual components of metabolic syndrome (MetS), such as hypertension and a waist circumference exceeding 102 cm, have been associated with an increased risk of PCa. Paradoxically, having three or more components of MetS has been linked to a reduced risk of the disease [38,39].

Obesity and Diabetes: Obesity is associated with a reduced risk of low-grade PCa, however, it heightens the risk of high-grade PCa[40]. Furthermore, obesity is correlated with increased PCa-specific mortality [41]. The basis of this intricate association is still not fully elucidated. The association between metformin and PCa, remains contentious. Although some studies suggest a reduced risk of PCa diagnosis among metformin users, these findings are not consistently reproduced across diverse populations [42].

Dietary Factors: The role of diet in PCa risk is multifaceted but remainsinconclusive. Some evidence suggests a potential protective effect of coffee [43], soy [44], and lycopene-rich foods, such as tomatoes[45], while other dietary elements like alcohol, red meat, and dairy products may elevate the risk of PCa development [46,47].

Hormonally Active Medications:5-alpha-reductase inhibitors (5-ARIs) have demonstrated potential in reducing the risk of low-grade PCa. However, their efficacy in preventing high-grade PCa remains ambiguous, and they may pose a small risk of high-grade cancer development [48]. Additionally, hormonal replacement therapy in hypogonadal men does not appear to elevate the risk of PCa, however, long term data is lacking [49].

Other Potential Risk Factors: Numerous additional risk factors have been explored, including inflammatory bowel disease, smoking, and occupational exposures, such as nightshift work[50,51]. Moreover, sexually transmitted infections like gonorrhea, and viral infections, including human papillomavirus, have been implicated in PCa development[52,53].

Staging and Classification

The goal of a tumour classification system is to stratify patients with similar clinical outcomes. This smoothens discussions with patients regarding prognosis and helps in designing clinical trials with more uniform patient populations. The Union for International Cancer Control (UICC) 8th edition (2017), the Tumour, Node, Metastasis (TNM) classification for staging of PCa [54] and the EAU risk group classification are commonly used[55].

The latter classification is centred on clubbing patients with a comparable risk of biochemical recurrence (BCR) following radical prostatectomy (RP) or external beam radiotherapy (EBRT). Modifications in diagnostic evaluation, such as enhancements in imaging (e.g., MRI, PSMA PET/CT scan) and biopsy techniques

(e.g., an increased number of systematic biopsy cores, targeted biopsy, cognitive biospy, fusion biopsy), may result in a shift in risk stratification systems[56].

The 2017 AJCC 8th edition emphasises that clinical staging should be derived from digital rectal examination (DRE) alone, a stance not in unison with the Union for International Cancer Control (UICC). The European Association of Urology (EAU) D'Amico risk group classification relies on DRE findings for clinical T-stage assessment. Imaging results, such as MRI, should be reported separately and not used for T-stage determination as per AJCC.

Table 1: Clinical Tumour Node Metastasis (TNM) classification of PCa [54]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically inapparent tumour that is not palpable
T1a Tumour incidental histological finding in 5% or less of tissue resected
T1b Tumour incidental histological finding in more than 5% of tissue resected
T1c Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2 Tumour that is palpable and confined within the prostate
T2a Tumour involves one half of one lobe or less
T2b Tumour involves more than half of one lobe
T2c Tumour involves both lobes
T3 Tumour extends palpably through the prostatic capsule
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumour invades seminal vesicle(s)
T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional (pelvic) Lymph Nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M - Distant Metastasis
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Gleason score and International Society of Urological Pathology 2019 grade

Originally, the Gleason grading system delineated five histological grades (1–5) for prostate cancer, but during the 2005 and 2014 ISUP consensus meetings, grades 1 and 2 were removed [57,58]. The revised 2005 Gleason score (GS) calculates the score by summing the most predominant (primary) pattern with the second most common (secondary) pattern in biopsy-detected prostate cancer. If only one pattern is evident, it is counted twice to compute the GS. In cases with three patterns, the score is derived from combining the most frequent and the highest grade, irrespective of the latter's extent. Moreover, the presence of intraductal carcinoma (IDC) alongside invasive prostate cancer is incorporated into the GS based on its architectural pattern [59]. Furthermore, a comprehensive GS may be calculated, incorporating the cumulative extent of each grade from all prostate biopsies. In later updates in 2014 and 2019, the ISUP further streamlined the grading system to five distinct grades, numbered from 1 to 5[60].

In RP specimens, using the Gleason system to grade conventional prostatic adenocarcinoma is crucial for predicting clinical outcomes and response to therapy[58]. The Gleason Score (GS) helps in disease-specific survival after prostatectomy and is included in relevant nomograms. The ISUP grade group for these specimens is assessed similarly to biopsies, except that minor high-grade components (<5%) are excluded from the ISUP grade group. For instance, if a carcinoma is mostly Gleason grade 3 but has a small Gleason grade 4 or 5 component (<5%), this component is excluded from the Gleason Score. The ISUP grade group for multifocal tumors is determined by the index lesion, which is the tumor with the highest grade, stage, or volume.

Table 2: International Society of Urological Pathology 2014 grade (group) system

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10 (4+5 or 5+4 or 5+5)	5

Table 3: EAU risk stratification for biochemical recurrence of localised and locally-advanced PCa (based on systematic biopsy)

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL Or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade) cT3-4 or cN+**
Localised			Locally advanced

. * Based on digital rectal examination.
** Based on CT/bone scan.

DIAGNOSTIC EVALUATION

Clinical Symptoms

Localised PCa is usually asymptomatic. Local progression may cause symptoms such as LUTS, erectile dysfunction (ED), urinary retention, pain, haematuria . Bone metastases may cause pain or spinal cord compression. Digital rectal examination (DRE) and PSA-are usually part of the initial diagnostic evaluation in these cases, after which a further staging workup may be initiated.

Digital Rectal Examination

Digital rectal examination (DRE) detects prostate cancer (PCa) in about 18% of cases, independently of PSA levels [61]. A suspicious DRE with a PSA level ≤ 2 ng/mL has a positive predictive value of 5–30% [61]. An abnormal DRE is also linked to a higher risk of clinically significant PCa under active surveillance, and it necessitates further evaluation with MRI and biopsy[62,63]. DRE is critical for T-staging and is a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4)[64].

Prostate specific antigen

Prostate-specific antigen (PSA), a glycoprotein enzyme secreted by prostate epithelial cells, is the primary marker for suspecting PCa[65]. While PSA is organ-specific, it is not cancer-specific; it may also be elevated in benign prostatic hyperplasia (BPH), prostatitis, Urinary tract infections, acute urinary retention and other non-malignant conditions. There are no definitive guidelines for defining PSA thresholds, reflecting its continuous nature, with higher levels indicating a greater likelihood of PCa. Some men may harbour PCa despite having low serum PSA levels [66,67].

PSA Density

Prostate-specific antigen density (PSA-D), the ratio of serum PSA to prostate volume, indicates a higher likelihood of clinically significant prostate cancer (PCa), especially with smaller prostates using a cut-off of 0.15 ng/mL/cc[68]. However, PSA-D's reliability is limited by inconsistent prostate volume measurements obtained via DRE, TRUS, or MRI. Studies show MRI measures prostate volumes more accurately than TRUS, which tends to underestimate by about 8%, while transabdominal ultrasound overestimates by 9.9 ml and is thus not recommended[69,70].

IMAGING

Magnetic Resonance Imaging

Multi-parametric MRI, integrating T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging, is done upon suspicion of PCa from PSA and/or DRE findings. It aids in detecting and local staging of PCa, targeting biopsies, and differentiating PCa from benign conditions using the PI-RADS scoring system on a 1-5 scale[71-73]. MRI has shown high sensitivity, particularly for detecting ISUP grade group ≥ 2 cancers larger than 10 mm, confirmed by Cochrane meta-analysis to have high sensitivity and moderate specificity compared to template biopsies[74,75].

Transrectal ultrasound and ultrasound-based techniques

Transrectal ultrasound (TRUS) is unsubstantiated for detecting PCa, with new ultrasound techniques like micro-Doppler, sonoelastography, or contrast-enhanced ultrasound showing initial potential [76-78]. The CADMUS trial compared mpMRI and ultrasound, finding that MRI detected slightly more csPCa with fewer unnecessary biopsies[79]. High-resolution micro-US, while less effective at assessing large prostate anterior parts, complements MRI in detecting PCa, especially with MRI/fusion biopsies [80-82].

PSMA-PET/CT or -PET/MRI, primarily for metastatic staging, has shown good sensitivity and specificity for csPCa detection and can guide targeted biopsies[83].

Biopsy Approach

Ultrasound (US)-guided prostate biopsy is the standard practice, though MRI in-bore biopsy is available at select centers. This biopsy can be administered via transperineal or transrectal routes, both under local anesthesia [84]. A systematic review and meta-analysis of eight studies found that MRI-targeted transperineal biopsy is more sensitive in detecting clinically significant prostate cancer (csPCa) compared to the transrectal approach (86%

vs. 73%), especially for anteriorly located tumors [85]. Additionally, the transperineal method is associated with a lower risk of infection [86,87].

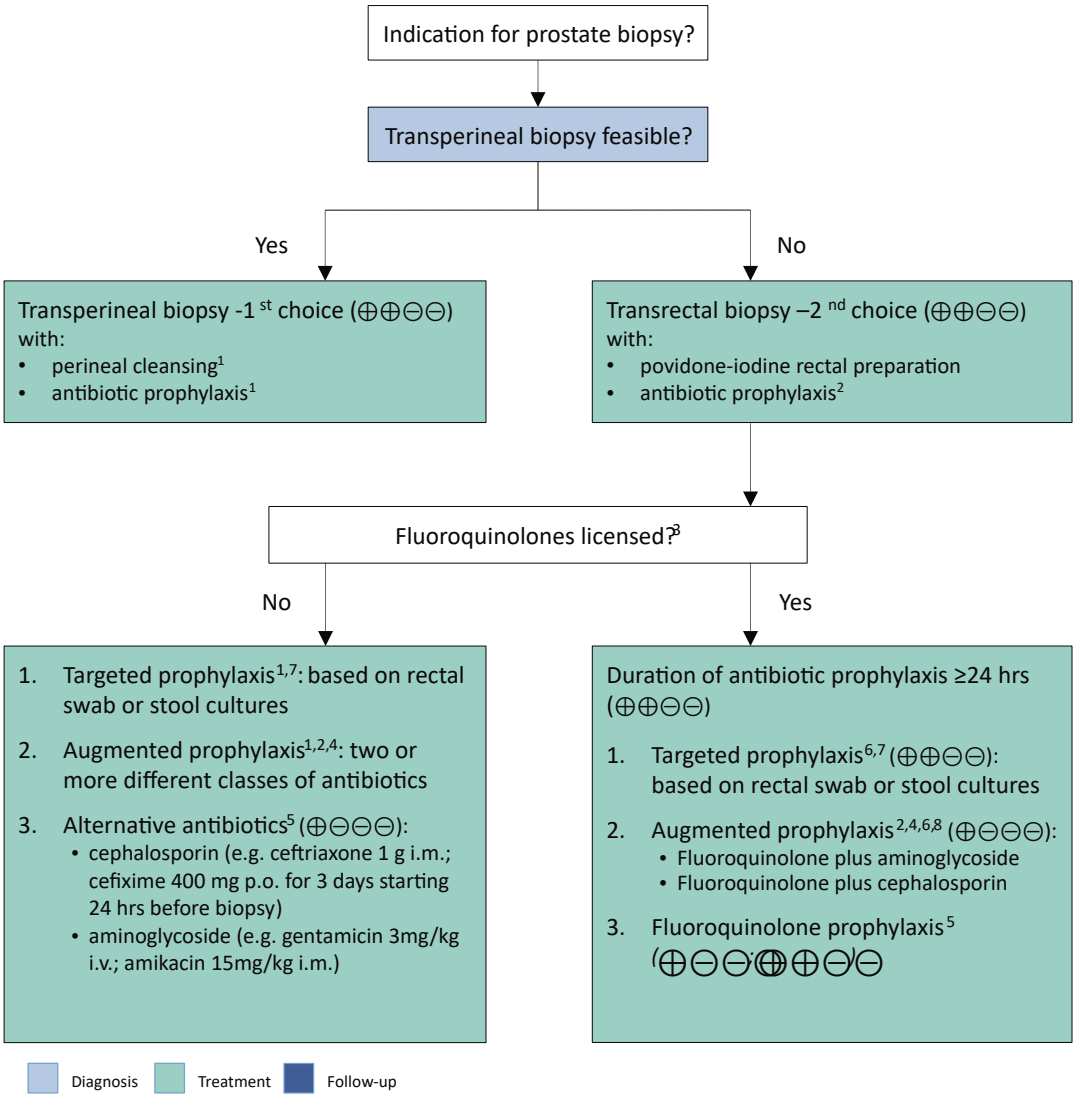
Indication for prostate biopsy?
Transperineal biopsy feasible?
Yes
No
Transperineal biopsy -1 st choice (⊕⊕⊖⊖) with:
• perineal cleansing1
• antibiotic prophylaxis1
Transrectal biopsy –2 nd choice (⊕⊕⊖⊖) with:
• povidone-iodine rectal preparation
• antibiotic prophylaxis2
Fluoroquinolones licensed?3
No
Yes
1. Targeted prophylaxis1,7: based on rectal swab or stool cultures
2. Augmented prophylaxis1,2,4: two or more different classes of antibiotics
3. Alternative antibiotics5 (⊕⊖⊖⊖):
• cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy)
• aminoglycoside (e.g. gentamicin 3mg/kg i.v.; amikacin 15mg/kg i.m.)
Duration of antibiotic prophylaxis ≥24 hrs (⊕⊕⊖⊖)
1. Targeted prophylaxis6,7 (⊕⊕⊖⊖): based on rectal swab or stool cultures
2. Augmented prophylaxis2,4,6,8 (⊕⊖⊖⊖):
• Fluoroquinolone plus aminoglycoside
• Fluoroquinolone plus cephalosporin
3. Fluoroquinolone prophylaxis5
Diagnosis
Treatment
Follow-up

Figure 1: Prostate Biopsy Flowchart

CLINICAL STAGING

T-staging

Clinical T-staging relies solely on DRE findings per TNM Classification and EAU risk categories, without considering imaging or biopsy results for local staging [88].

For locally advanced cancers, abdominopelvic CT may reveal rectal or bladder invasion and Dilatation of upper tracts [89].

Magnetic Resonance Imaging

T2-weighted MRI remains of utmost importance for local prostate cancer staging, offering differential sensitivity and specificity across various cancer stages. The high-resolution capabilities of a 3 Tesla MRI notably enhance the accuracy in detecting extraprostatic extension (EPE) and seminal vesicle invasion (SVI), pivotal for assessing advanced disease stages [90]. However, despite its superior imaging quality, the utility of MRI in low-risk prostate cancer cases is generally not adviseable.

MRI in Clinical Practice

MRI significantly outperforms DRE in sensitivity for identifying non-organ confined disease, thus refining risk categorisation and improving predictive accuracy for postoperative outcomes, such as BCR-free survival[91]. The integration of MRI findings into multivariate risk calculators augments their ability to predict pathological stages, including extraprostatic extension, seminal vesicle invasion, or positive surgical margins. These enhanced predictions facilitate more customised and effectual treatment planning[92].

N-staging

Computed Tomography and MRI

CT and MRI use lymph node (LN) size and morphology to assess nodal invasion, with varying effectiveness. LNs larger than thresholds are typically considered malignant, but the ideal size threshold remains unresolved[93,94].

Risk Calculators

Nomograms incorporating clinical and MRI data are used to estimate the risk of positive LNs, with recent models integrating MRI-targeted biopsy findings showing promising results [59,95].

M-staging

Bone Scan

Bone scans are highly sensitive and influenced by PSA levels, tumor grade, and clinical stage, with significant potential for detecting metastases[96,97].

Advanced Imaging Techniques

Fluoride PET/CT and diffusion-weighted MRI are more sensitive than traditional bone scans for detecting bone metastases, also allowing for the detection of other metastatic sites[98,99].

PSMA PET/CT

PSMA PET/CT offers improved sensitivity and specificity for LN staging over conventional imaging, influencing clinical decision-making and potentially avoiding unnecessary LN dissections[100,101]. Emerging evidence suggests replacing traditional bone scans and CT with more sensitive imaging techniques like choline PET/CT, PSMA PET/CT, and whole-body MRI for initial N/M staging in high-risk PCa.

Defining Locally Advanced and Oligometastatic Carcinoma Prostate

Currently, there is no recognised definition for locally advanced prostate cancer. The term is generally used to describe a spectrum of disease states that can include any of the following characteristics:

Clinical stage as defined by the American Joint Committee on Cancer (AJCC) includes T3 (tumors extending to the periprostatic area or into seminal vesicles), T4 (larger tumours invading the external sphincter, bladder neck, rectum, levator ani muscles, or anchored to the pelvic sidewall), or N1 (regional pelvic lymph node involvement at any local T stage), all without signs of distant metastases M0[102].

Hellman and Weichselbaum initially proposed the concept of an oligometastatic state, identifying it as a subgroup of patients with a limited number of detectable metastases who may still have a potentially curable condition[103,104].

Two prevalent criteria, LATITUDE[105] and CHAARTED[106], serve as benchmarks for defining high-risk prostate cancer. The LATITUDE criteria classify a tumour as high-risk if it meets at least two of the following conditions: the presence of three or more bone metastases, any visceral metastases, or an ISUP grade of 4 or higher[105]. The CHAARTED trial identified patients with high volume disease as those having four or more bone metastases, which must include at least one metastasis outside of the axial skeleton (vertebral column or spine), or any visceral metastases [106]. These definitions are also integrated into the prostate cancer guidelines issued by the European Association of Urology [107].

Table 4: Criteria for Defining OMPCa

	High	Low
CHAARTED (volume)	≥ 4 Bone metastases including ≥ 1 outside vertebral column or pelvis AND/OR Visceral metastasis*	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

The impact of advanced imaging techniques like 68Ga-PSMA, 18F-PSMA, and 18F-fluciclovine PET/CT on defining OMPCa is still uncertain. These methods may lead to a revised definition of OMPCa in the future, potentially considering not just the number of lesions but also their size and standardised uptake value (SUV).

Role of RLT in Locally Advanced Carcinoma Prostate

Due to the lack of definitive evidence, a systematic review was unable to determine the most effective treatment strategy in patients with locally advanced disease[108]. Currently, only external beam radiation therapy (EBRT) has been evaluated in randomised controlled trials. Combining local with systemic treatment appears to yield superior results, assuming the patient's performance status allows for both treatments. Preliminary data from the SCPG-15 trials indicate that randomising between surgery and EBRT is feasible, although the oncological results are still awaited[109].

Surgery for LAPC as part of multimodality approach has been elucidated[110-112] .The comparative oncological success of RP as part of multimodal treatment strategy versus upfront EBRT with ADT for locally advanced prostate cancer remains unsubstantiated, although a prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against EBRT with ADT among patients with LAPC is underway[113,114].

Even in cases of suspected positive lymph nodes during surgery in an otherwise clinically N0 patient based on preoperative imaging the procedure should not be deferred as RP may offer survival benefit in these patients[115].

The management of clinically node positive disease without any metastases has been based primarily on long term ADT coupled with local therapy. A systemic review of five studies highlighted the benefits of adding local therapy (RT or RP) in terms of OS and CSS in this subset of patients[116].

Two randomised controlled trials within the STAMPEDE platform protocol examined men with newly diagnosed high-risk/locally advanced M0 disease or those relapsing post-curative therapy with high-risk features, where 39% of the patients (n = 774) presented with N1 disease based on conventional imaging[117]. Among these, 71% received RT in conjunction with long-term ADT. Considering the metastasis-free survival (MFS) and overall survival (OS) advantages seen in the broader study group, a standard of care (SOC) in cN1 patients should involve combined ADT (for three years) and abiraterone (for two years), alongside prostate and whole pelvic radiotherapy (WPRT).

Adjuvant Androgen Ablation in pN1 Disease: Combining RP with early adjuvant hormone therapy (HT) in patients with pN+ prostate cancer (PCa) has demonstrated a 10-year cancer-specific survival (CSS) rate of 80%, with significant improvements in CSS and overall survival (OS) substantiated in prospective randomised controlled trials (RCTs) [118,119]. However, these studies included patients with high-volume nodal disease and multiple adverse tumour features, which may limit the applicability of results to those with less extensive nodal involvement.

Adjuvant Radiotherapy Combined with ADT in pN1 Disease: A retrospective multi-centre cohort study found that administering RT to the prostatic fossa, combined with ongoing ADT, within six months post-surgery, enhances local control in PCa patients with pN1

following RP. This combination particularly benefits survival in men with low-volume nodal disease (fewer than 3 lymph nodes involved), higher ISUP grade groups (2-5), and more advanced local disease (pT3-4 or R1). However, it appears less efficacious in other subgroups[120].

Observation of pN1 Patients Post-Radical Prostatectomy: Management strategies for pN1 PCa post- RP and ePLND has been explored in several retrospective studies and a systematic review[121-125]. Findings suggest that a subset of patients with minimal nodal involvement (1-2 positive lymph nodes) experience favourable oncologic outcomes without the need for additional treatment.

For instance, the STAMPEDE trial, a well-known RCT, evaluated the impact of local therapy in advanced prostate cancer. The trial concluded that local control through EBRT, combined with systemic treatments such as ADT and abiraterone, led to improved survival outcomes in patients with a limited metastatic burden[8]. They also deduced survival benefit for men with pelvic lymph node positive disease (TanyN1M0)[8].

Summary Flow for Adjuvant Radiation Therapy in Locally Advanced Prostate Cancer

1. pN0 Patients

- No ADT ⟶ If ISUP 4–5 & pT3 ± margins ⟶ Adjuvant radiation (IMRT/VMAT + IGRT)

2. pN1 Patients

- Extended lymph node dissection ⟶ Three options:

A. ADT

B. ADT + IMRT/VMAT + IGRT

C. Observation (if < 2 nodes and PSA < 0.1 ng/mL)

Management of Metastatic Prostate Cancer

It is imperative to mention that all prospective evidence currently at hand depend on the definition of M1 disease based on CT scan, MRI and bone scintigraphy. The effect of newer imaging modalities like PSMA on treatment and outcome is yet to be fully elucidated.

The median survival of patients with newly diagnosed metastases (mHSPCa) is about 50 months if ADT alone is given. This, however, is highly variable since the M1 population is extremely heterogenous[126]. Various prognostic factors like number and site of bone metastases, visceral metastases, ISUP grade group, performance status, serum PSA at presentation, have been studied but have not been fully validated[127].

Primary ADT has been SOC for over 50 years. No compelling evidence supports one form of ADT over another on oncological outcomes, whether orchiectomy or LHRH agonists/antagonists. However, testosterone levels drop more rapidly with orchiectomy and LHRH antagonists, making them suitable for patients at risk of complications like spinal cord compression. Some studies and meta-analyses suggest LHRH antagonists may cause fewer cardiovascular side effects compared to agonists, so they may be appropriate in patients with cardiovascular disease[128-130]. Based on the SWOG 9345 trial results the use of intermittent ADT has been superseded as continuous ADT based combination therapies has become SOC[131].

Three pivotal randomised controlled trials (RCTs) were conducted, each evaluating the efficacy of ADT alone, the standard of care (SOC), versus ADT combined with early administration of docetaxel (75 mg/m^2, administered every three weeks within three months of ADT initiation). The primary endpoint across all studies was overall survival (OS), with the key results outlined in Table 5. These trials aimed to determine whether the

addition of chemotherapy to ADT could significantly improve patient outcomes in terms of survival and disease progression[132,106,133].

Table 5: Comparative Table Of RCTS

	STAMPEDE[132,132]		**GETUG-AFU 15 [133]**		**CHAARTED [106]]**	
	ADT	ADT + Docetaxel (6 cycles) + P	ADT	ADT + Docetaxel (9 cycles)	ADT	ADT + Docetaxel (6 cycles)
N	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%
Key inclusion criteria	Patients scheduled for longterm ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL, or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥ 70%		Metastatic disease ECOG PS 0, 1 or 2	
Primary objective	OS		OS		OS	
Median follow up (mo)	43; 78.2 (update M1)		50		54 (update)	
N	1,086		-		-	
HR (95% CI)	0.81 (0.69-0.95)		-		-	

CI = confidence interval; HR = hazard ratio;mo = month; n = number of patients; OS = overall survival; P = prednisone;

Based on this data, upfront docetaxel combined with ADT became a standard treatment for men with newly diagnosed metastatic prostate cancer, provided they were fit for chemotherapy. However, two recent large Phase III trials have shown an overall survival (OS) benefit when adding an androgen receptor pathway inhibitor (ARPI) to ADT and docetaxel. As a result, docetaxel should only be added to ADT alone if ARPIs are unavailable or contraindicated[135].

Role of RLT in Oligometastatic Carcinoma Prostate

The volume of disease as a potential prognostic factor was first introduced in the CHAARTED (chemo-hormonal therapy versus androgen ablation randomised trial for extensive disease in prostate cancer)[106] and later, in STAMPEDE , was shown to be prognostic in a subgroup analysis for benefit of supplementation of prostate RT to ADT in a cohort of patients with low volume/ oligometastatic disease[8].

The TRoMbone trial(Testing Radical Prostatectomy in Men with Oligometastatic Prostate Cancer), a feasibility study, explored the role of surgery in OMPCa. This study provided early evidence suggesting that RP, in combination with systemic therapies like ADT, leads to a significant decline in serum PSA levels and offers potential survival benefits[7]. Early results indicated that the combination of surgery with systemic therapies, (ADT and chemotherapy) led to a significant decline in serum PSA levels, suggesting effective local control of the disease[7].

OMPCa with respect to this study was defined as one to three osseous metastases without visceral involvement. This trial was designed as a prospective, randomised, non-blinded feasibility study conducted across nine high-volume robotic surgery centres in the UK. The study's objective was to randomise 50 men with synchronous OMPCa to receive either standard systemic therapy, including ADT with or without chemotherapy, or standard therapy plus RP with pelvic lymphadenectomy. Recruitment was supported by the QuinteT Recruitment Intervention (QRI), a framework designed to overcome recruitment barriers in clinical trials[7].

The primary outcome of the study was to assess the feasibility of recruiting patients into the trial, while secondary outcomes focused on perioperative safety, quality of life (QoL), and early functional and oncological outcomes. Quality of life was measured using the

EuroQoL five-dimension five-level (EQ-5D-5L) questionnaires[136], and clinical outcomes included PSA levels, surgical complications, continence, and erectile function.

Results showed that recruitment was successful, with 51 men randomised over 14 months, surpassing the expected recruitment timeline. The trial demonstrated that it is feasible to randomise patients to undergo RP in the setting of OMPCa.

In terms of safety, the study showed that RP in this subset of patients was safe, with complication rates and perioperative outcomes akin to those seen in surgeries for localised PCa. No major adverse events were recorded, and the surgeries were successfully completed without the need for conversions or deferred procedures. Postoperatively, urinary continence recovery was identical to that seen in patients undergoing RP for localised disease, though a small proportion of patients (16.7%) remained incontinent at six months. Erectile function was not preserved in most patients, which was anticipated given the high-risk nature of disease[7].

Oncologically, the study provided promising early results. At six months postoperatively, 82.6% of patients in the RP group had a PSA level below 1 ng/mL, indicating good biochemical control. However, the positive surgical margin rate was 41.7%, reflecting the difficulty in complete resection owing to the advanced nature of the disease in this patient population[7].

The HORRAD trial was the first reported trial evaluating the role of RT in men with metastatic castration sensitive disease, aimed to determine whether adding EBRT to ADT improves outcomes for patients with metastatic prostate cancer (mPCa). The trial enrolled 432 patients with PSA levels above 20 ng/ml and bone metastases between 2004 and 2014. Patients were randomised to receive either ADT alone or ADT with EBRT. The primary endpoint was overall survival, and the secondary endpoint was time to PSA progression[12].

The results showed no significant difference in overall survival between the two groups: 45 months in the RT group and 43 months in the control group (p=0.4). However, time to PSA progression was longer in the RT group (15 months vs. 12 months, p=0.02), indicating some benefit in delaying disease progression. The trial found no overall survival advantage from adding EBRT to ADT, although the confidence interval did not rule out the potential for a survival benefit.Additionally, a retrospective analysis in the trial found that radiotherapy reduced local PCa related events, such as bladder obstruction and surgical interventions, and extended the time to these interventions compared to ADT alone. While the study did not show a clear survival benefit, it suggested that EBRT may help reduce local complications and delay disease progression[12].

The STAMPEDE trial, a large-scale randomised phase 3 study conducted at 117 hospitals in the UK and Switzerland, was designed to examine whether adding RT to standard systemic therapy could enhance outcomes in men with newly diagnosed metastatic prostate cancer. A total of 2061 participants were randomised to either receive SOC—comprising ADT with or without docetaxel—or standard care plus RT directed at the prostate[8].

The primary aim of the trial was to evaluate if RT could improve overall survival (OS), while secondary measures focused on failure-free survival (FFS), progression-free survival (PFS), and the incidence of local events related to cancer progression[8]. A key aspect of the study was the classification of metastatic burden, using the CHAARTED criteria, which differentiates between low metastatic burden (fewer than five bone metastases without visceral involvement) and high metastatic burden[106].

After a median follow-up period of 37 months, the results indicated that RT did not provide a significant improvement in overall survival across the entire study population. However, in patients with a low metastatic burden, RT demonstrated a significant survival benefit,

with an HR of 0.68 (95% CI: 0.52–0.90; p = 0.007), resulting in a 3-year survival rate of 81% for the RT group compared to 73% in the control group[8].

Moreover, RT significantly extended failure-free survival for the entire cohort (HR 0.76, 95% CI: 0.68–0.84; p < 0.0001), with more pronounced benefits observed in the low-burden group. Radiotherapy was generally well tolerated, with only 5% of patients experiencing grade 3 or 4 acute toxicities, primarily affecting the bladder and bowel[8].

HORRAD and STAMPEDE are published phase 3 trials that have drawn a comparison between prostate directed RT versus the standard of care in patients with metastatic disease

Both the studies did not show any difference between those patients who received RT to the prostate coupled with ADT and those who received ADT alone in the preliminary results. However, a post hoc subgroup analysis in both the studies depicted survival benefit in patients with low metastatic burden[,8,12]. The STOPCAP meta-analysis of the STAMPEDE and HORRAD utilised the HORRAD definitions for low and high metastatic burden (low burden disease in HORRAD was defined as less than or equal to 4 bony metastases)[137]. The meta-analysis concluded that the three-year survival in patients with less than or equal to 4 osseous lesions was 77%. This was in contrast to 70 % when the STAMPEDE definition was incorporated[8,12,137].

Table 6: Comparison of the HORRAD and STAMPEDE Trials [8,12]

	HORRAD Post hoc subgroup analysis	STAMPEDE
Number of patients with low-burden disease	160	819
De novo or recurrent disease?	De novo	De novo
Definition of low-burden disease	%4 osseous lesions	<4 osseous metastases, none outside the vertebral bodies or pelvis; no visceral metastases
Imaging modality used to stage disease	Bone scan	Bone scan and CT
Intervention Control	RT to the prostate + ADT ADT	RT to the prostate + ADT ADT
Median follow-up	47 mo	41.9 mo
HR for all-cause mortality (intervention vs control)	HR, 0.68; 95% CI, 0.42-1.10	HR, 0.68; 95% CI, 0.52-0.90

HR, hazard ratio; mo, months.

Madhavan et al., in their meta-analysis of three (RCTs), reinforced the robust significance of RLT, with particular emphasis on the therapeutic benefits of EBRT in patients with OMPCa. However, they advised guarded interpretation of these findings due to the limited number of studies and the relatively small sample sizes, especially RP subgroup[138]. The analysis included the HORRAD and STAMPEDE trials, alongside a study by Dai et al[11,16,139]. In the intervention group, the STAMPEDE trial employed EBRT to the prostate, administering

either a total dose of 36 Gy across six weekly fractions of 6 Gy or 55 Gy in 20 daily fractions of 2.75 Gy over four weeks. The HORRAD trial similarly applied EBRT to the prostate within three months of initiating ADT, delivering either 70 Gy across 35 fractions of 2 Gy or 57.76 Gy in 19 fractions of 3.04 Gy, three times per week for six weeks. In contrast, Dai et al. performed cytoreductive radical prostatectomy—either open or laparoscopic—with or without lymph node dissection or administered IMRT at a dose of 74 Gy in 37 fractions. For those with pelvic lymph node metastases, an additional 45 Gy in 18 fractions was directed to the affected lymph nodes. Notably, all three trials demonstrated significantly improved overall survival in the intervention arms[8,12,139].

The outcomes of other key trials, such as the Best Systemic Therapy (BST) or Best Systemic Therapy Plus Definitive Treatment (Radiation or Surgery) trial, as well as the PEACE-1 trial, which explore the efficacy of RLT in comparison to SOC, are awaited[140,141]. Additionally, several other trials, including the Surgery in Metastatic Carcinoma of Prostate (SIMCAP) trial, SWOG1802, are currently in the recruitment phase, promising further insights into this critical therapeutic area[142].

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AIMS & OBJECTIVES.

HYPOTHESIS: Radical local therapies, i.e, Radical Prostatectomy or EBRT, are an efficacious treatment modality in the management of patients with locally advanced and oligometastatic carcinoma prostate.

Aim: To assess the efficacy of radical local therapies, i.e, EBRT or Radical Prostatectomy in patients with locally advanced and OMPCa.

Primary objective:

1. To ascertain the response of local therapy in terms of decline in serum psa at 3 months following EBRT and Radical Prostatectomy in patients with locally advanced or OMPCa.

MATERIALS & METHODS

Study design: - This was a Prospective, observational study.

Institute: The study was conducted at the All-India Institute of Medical Sciences, Bhopal, in the Department of Urology. (March 2023- September 2024).

Conflict of interest: Nothing to disclose.

Ethical Clearance: Ethical clearance was obtained from the Institutional Human Ethics Committee (IHEC)- Student Research of AIIMS Bhopal. (AIIMS/BPL/IHECSR/July/22/SS/09). Date:28/02/2023

Study population -This prospective study was conducted from March 2023 till September 2024 on biopsy proven cases of carcinoma prostate after issue of letter of permission. The patient's befitting the inclusion and exclusion criteria were admitted from Urology and Radiotherapy OPD. The patients were then given the informed consent sheet and patient information sheet. This being a non interventional observational study, hence, the local therapy (EBRT or Radical Prostatectomy) to be administered was at the treating physician's discretion after shared decision making.

Inclusion Criteria

Patients with biopsy proven CA prostate with the following: -

T3a and above or N1

or

Oligometastatic disease defined on the basis of bone scan or PSMA PET scan as <= 5 bone metastases without any visceral metastases

Serum PSA > 20 nanogram per ml or a combination of any of the above and with the following parameters:

Age 40 - 80

Performance Status ~ ECOG 2 or less

Life expectancy > 10 y as per WHO life tables

Exclusion Criteria

The exclusion criteria are as follows:

1. Any other histological subtype other than adenocarcinoma of the prostate
2. Any prior radical local treatment or radiotherapy
3. Visceral metastases
4. Contraindication to radical prostatectomy or prior RT to abdomen and pelvis

Study duration: 18 Months

*PSMA PET was not available at AIIMS, Bhopal at the time of conduct of this study.

EBRT Protocol for Locally Advanced and OMPCa

EBRT is one of the pillars in the multimodality management of LAPC and OMPCa[143]. This protocol encompasses sophisticated treatment planning, dose fractionation, and integration with ADT, leveraging the latest clinical evidence and guidelines.

Initial Consultation and Assessment

The treatment journey began with a thorough patient evaluation, including a detailed medical history, physical examination, and review of diagnostic imaging and biopsy results. During this phase, the multidisciplinary team assessed the extent of prostate cancer, categorising it into locally advanced or oligometastatic stages based on TNM staging and other prognostic factors. This assessment guides the later treatment decisions and planning.

Treatment Planning and Delivery

The first phase of EBRT involved systematic treatment planning, using cross-sectional imaging to delineate the target and adjacent critical structures accurately. The advent of technical innovations such as IMRT and VMAT with IGRT, has significantly enhanced the precision and conformality of radiation delivery. These advancements allow for escalated radiation doses to be delivered directly to the prostate while minimizing exposure to surrounding normal tissues, thus improving the therapeutic ratio[144,145].

Radiation Simulation, Computed Tomography (CT) and Technical Aspects

Prior to EBRT, a critical step involves the radiation simulation and CT scanning to ensure accurate target delineation and patient positioning. The patient is positioned comfortably on a thermoplastic board made of carbon fibre, designed to minimise movement during treatment. This board is customised with markings corresponding to specific anatomical

zones and landmarks, ensuring reproducibility and precision throughout the treatment course. The immobilisation achieved with custom-molded thermoplastic casts further enhances the accuracy of radiation delivery, as these are tailored to the patient's body and bony landmarks.

IMRT and VMAT employ dynamic multi-leaf collimators, which continuously adapt to the contours of the target volume seen by each beam. Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT-scanning[144,145].

Dose Fractionation:

The traditional approach to EBRT involved conventional fractionation, typically administering doses ranging from 1.8 to 2.0 Gy per fraction. There is a growing body of evidence which supports the efficacy of hypofractionated regimens, which involve larger doses per fraction over a shorter period[144,145].

Fractionated RT leverages the different DNA repair capacities between normal and tumor tissues. Slowly proliferating cells, characteristic of prostate cancer (PCa), are particularly sensitive to higher doses per fraction. A meta-analysis of 25 studies involving more than 14,000 patients concluded that hypofractionated RT, delivering 2.5–3.4 Gy per fraction, could be more effective than conventional doses of 1.8–2 Gy for PCa due to its slow growth rate[144,145]. Hypofractionation also improves patient compliance due to its reduced cost and shorter duration of treatment. For a subset of patients in our study prostate cancer, fractionation schemes such as 60 Gy in 20 fractions or 70 Gy in 28 fractions were utilised which have been supported by substantial clinical data. These regimens were chosen based on their balance of efficacy and patient convenience without compromising cancer control or increasing toxicity.

Integrating Androgen Deprivation Therapy (ADT):

EBRT was often combined with ADT to improve outcomes. The integration of long-course ADT (ranging from 18 to 36 months) with EBRT has shown to enhance cancer-specific survival rates significantly. ADT was typically initiated neoadjuvantly, concurrently, or adjuvantly, with the timing and duration influenced by individual patient factors and disease characteristics. The POP-RT trial highlighted the benefit of combining whole pelvis radiation with ADT, demonstrating significant improvements in biochemical failure-free survival and distant metastasis-free survival, despite no observed benefit in overall survival[143,146].

Safety and Side Effects:

While EBRT is a well-tolerated treatment with a reasonable morbidity profile, it is not devoid of potential side effects. Late grade II gastrointestinal toxicity were more prevalent with whole pelvis radiation. Therefor one must balance these considerations, employing modern radiation techniques to mitigate these risks effectively.

Ongoing Monitoring and Adjustment:

Throughout the course of radiation therapy, patients were regularly evaluated to monitor the response to treatment and assess any side effects. Adjustments to the radiation plan were made based on interim assessments. This proactive monitoring helped in managing any acute reactions and in adapting the treatment strategy as needed to refine patient outcomes.

Post-treatment Follow-up:

After completing EBRT, patients enter a follow-up phase, which is crucial for monitoring potential late effects of treatment and detecting any signs of recurrence. Regular follow-up visits typically included clinical evaluations, PSA tests, and imaging studies to ensure continued cancer control. This comprehensive approach to EBRT in LAPC and OMPCa ensures that each patient receives personalised, precise, and effective treatment.

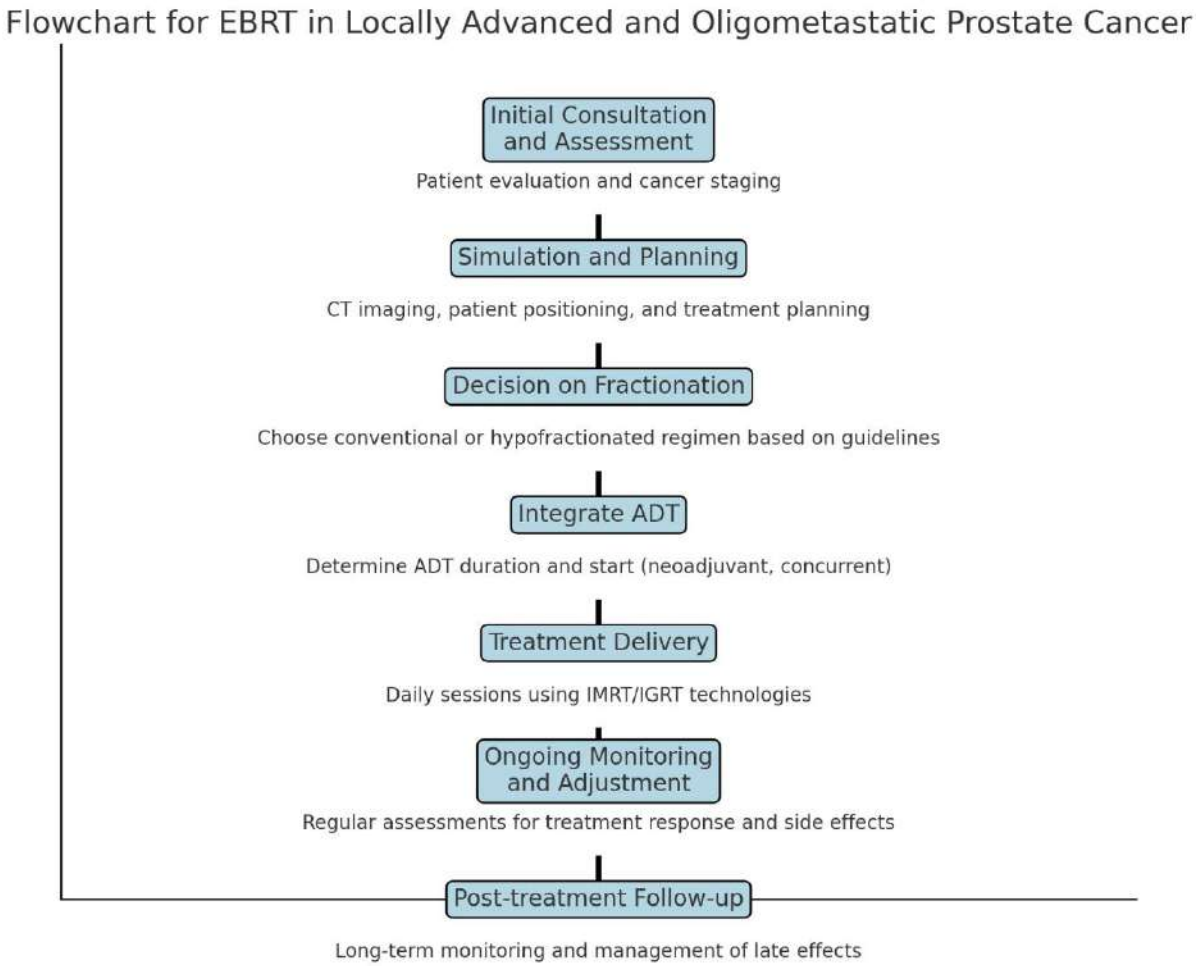
Flowchart for EBRT in Locally Advanced and Oligometastatic Prostate Cancer
Initial Consultation and Assessment
Patient evaluation and cancer staging
Simulation and Planning
CT imaging, patient positioning, and treatment planning
Decision on Fractionation
Choose conventional or hypofractionated regimen based on guidelines
Integrate ADT
Determine ADT duration and start (neoadjuvant, concurrent)
Treatment Delivery
Daily sessions using IMRT/IGRT technologies
Ongoing Monitoring and Adjustment
Regular assessments for treatment response and side effects
Post-treatment Follow-up
Long-term monitoring and management of late effects

Figure 2: Flowchart of EBRT in Locally Advanced and OMPCa

In conclusion, the protocol for EBRT in the treatment of locally advanced and OMPCa involves a combination of precise treatment planning, appropriately chosen fractionation schemes, and the strategic use of ADT.

Principles of Radical Prostatectomy

Approaches

Open Or Laparoscopic

Radical Retropubic Prostatectomy with Bilateral Pelvic Lymph Node Dissection

Once the patient was confirmed as an appropriate candidate for surgery befitting the inclusion criteria, preanesthetic checkup was done to obtain clearance for surgery. The patient then underwent an appropriate preoperative preparation to minimise complications and to facilitate operative success.

Preoperative

The standard preoperative regimen consisted of an extended office visit where in the patient was explained the risks, benefits, and potential alternatives of the procedure. The patient received details of the laparoscopic technology in the form of patient-centred brochures and was directed to the institution's website, which contains extensive information on what the patient should expect before, during, and after the procedure.

The standard surgical consent form emphasised on the complications that are inherent to laparoscopic techniques. The priorities of the procedure were also emphasised, including patient safety, preservation of the oncologic integrity of the procedure, and an attempt at performing the procedure laparoscopically. The risk of conversion to an open procedure was explained thoroughly in the framework of this group of priorities. Specifically, if the

patient's safety or the oncologic integrity of the operation is jeopardised, the attending surgeon may decide to convert the procedure to the open surgical technique.

Enhanced recovery after surgery protocols was followed. On the day of surgery, a preoperative enema was performed, sequential compression stockings were placed, and a large-bore intravenous line was begun with preoperative antibiotics that cover both genitourinary and skin flora.
Recommended prophylactic regimens- Second generation cephalosporin or aminoglycoside with metronidazole.

Intraoperative

Anesthesia: General endotracheal anaesthesia was the preferred anaesthesia with relative hypotension. Systolic blood pressure of no more than 100 mm Hg and to limit the replacement of crystalloid to 1500 mL until the prostate is removed.

Position: The patient was placed in the supine position when undergoing open prostatectomy whereas steep trendelenberg was the preferred position during laparoscopic prostatectomy.

Incision: An extra-peritoneal, lower abdominal incision was made extending from the pubis toward the umbilicus in cases of open prostatectomy.

Essential Steps

1) Exposure of the right and left pelvic paravesical and paraprostatic areas via a retroperitoneal approach.
2) Perform bilateral pelvic lymph node dissections and incision of the endopelvic fascia.

3) Ligation of the dorsal vein complex, avoiding damage to the striated sphincter, and meticulous hemostasis.

4) Transection of the urethra at the prostatic apex and incision of the prostatic fascia anteriorly to avoid the neurovascular bundles bilaterally. For some patients, a bladder neck sparing technique was employed to potentially improve postoperative urinary function.

5) Dissection and removal of the prostate and seminal vesicles en bloc.

6) Fashioning a new bladder neck that would accommodate the tip of the surgeon's index finger.

7) Performing a watertight urethrovesical anastomosis.

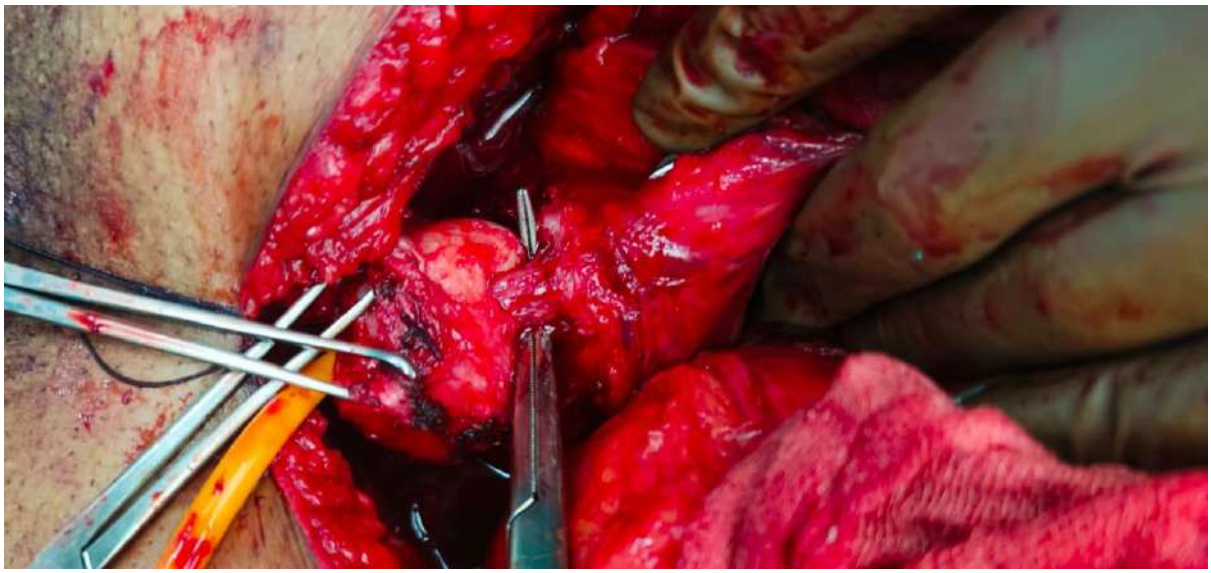

Figure 3: Bladder neck sparing approach

Post operative

Pain control: was usually achieved using NSAIDS. Narcotics were avoided wherever possible as they tend to exacerbate post op ileus. Patients were offered a clear liquid diet on post operative day 1 and a regular low-fat diet the following day.

Drains: if placed for evacuation of an unanticipated urine leak or lymphatic fluid collection, were typically removed between post operative day 3 to 5, unless patient specific factors necessitated longer drainage.

Urethral catheter: The duration of time required for the urethral catheter was dependent to a great extent on the preferred approach of the surgeon and the extent of bladder neck reconstruction. The 2-week period was commonly recommended for open surgery or laparoscopic surgery.

Return to normal activity following catheter removal at 1 week, patients would spend the next week recovering without particular restriction of activity. Most patients were able to return to all normal physical activity by 4 to 6 weeks. Strenuous exercise recommenced at 6 weeks.

STATISTICAL ANALYSIS

The data was tabulated in MS EXCEL spreadsheet and analysis was done using IBM Statistical Package for Social Sciences (SPSS) for Mac, version 23 (IBM Corp., Armonk, N.Y., USA.)

Descriptive statistics were presented as means and standard deviations or medians with interquartile ranges for continuous variables, and as frequencies and percentages for categorical variables. Data visualization was applied where suitable, using histograms, box-and-whisker plots, and column charts for continuous variables, and bar or pie charts for categorical variables. Comparisons between groups for continuous data were conducted using the independent sample t-test for two groups, while non-normally distributed data were analyzed with the Wilcoxon test. The Chi-squared test was used for comparing categorical data between groups, but if more than 20% of the cells in the contingency table had expected frequencies below 5, Fisher's Exact test was applied. For assessing the relationship between two continuous variables, Pearson's correlation was used for normally distributed data, while Spearman's correlation was applied to non-normally distributed data. Statistical significance was set at $p < 0.05$.

For Paired Analysis:

Paired analysis of continuous variables was performed using the paired t-test when comparing two variables. If the data were non-parametric, the Wilcoxon Signed Rank test was used instead. For comparisons involving more than two continuous variables, repeated measures ANOVA or the Friedman test was applied.

Categorical variables like stage of the disease, are presented in number and percentage (%) and continuous variables like age of the patient, serum psa levels are presented as mean ± SD and median.

1. Change in serum PSA has been compared using paired t test or Mann Whitney test.
2. Correlation between change in serum PSA and other continuous variables has been done using the Pearson or Spearman coefficient.
3. Correlation between change in serum PSA and other categorical variables has been done using the student T test/ Mann Whitney or Anova test.

RESULTS

This section provides a detailed analysis of the outcomes from our prospective observational study, aimed at evaluating both the biochemical and clinical impact of radical local therapies in patients diagnosed with locally advanced and OMPCa. The study featured two distinct treatment arms: radical prostatectomy and radiotherapy, with patient allocation based on disease characteristics fulfilling the inclusion criteria. A total of 30 participants were enrolled, with 73.3% undergoing radical prostatectomy and 26.7% receiving radiotherapy between March 2023 and September 2024. This relatively modest sample size reflects the study's focus on a targeted patient population with locally advanced or oligometastatic disease. Despite the sample size, the findings offer valuable insights into the comparative effectiveness of these two treatment modalities, particularly in terms of biochemical outcomes such as PSA decline and other clinical parameters. The results are presented by exploring the baseline demographic and clinical characteristics, including age, initial PSA levels, PIRADS scores, ISUP grades, and TNM staging. Additionally, short-term biochemical responses, PSA at three months as well as change in PSA are analyzed in relation to T stage, nodal involvement, metastatic burden, surgical margins which serve as key clinical determinants of treatment success.

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DESCRIPTIVE PARAMETERS

Distribution of the participants in terms of Radical Local Therapy

Management	Frequency	Percentage	95% CI
Radical Prostatectomy	22	73.3%	53.8% - 87.0%
Radiotherapy	8	26.7%	13.0% - 46.2%

73.3% of the participants in the study underwent Radical Prostatectomy.

26.7% of the participants underwent Radiotherapy.

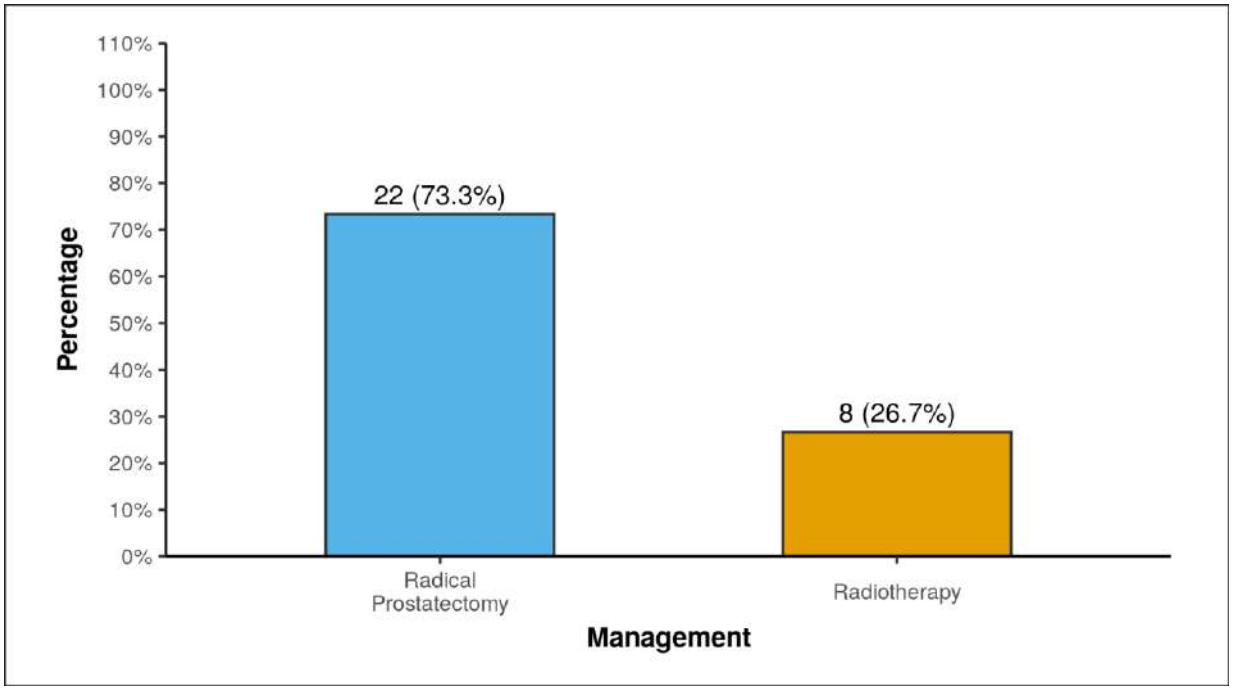


Figure 4: Distribution of Participants in terms of RLT

Distribution of the Participants in Terms of Age in Years

Age (Years)	
Mean (SD)	64.03 (7.89)
Median (IQR)	65 (61.25-69.5)
Range	45 - 76

The mean (SD) of Age (Years) was 64.03 (7.89). The median (IQR) of Age (Years) was 65.00 (61.25-69.5). The Age (Years) ranged from 45 - 76.

The skewness of the data was -0.66, and it suggested that the data was negatively skewed, thus suggesting it was not normally distributed. The kurtosis of the data was -0.33, and it suggested that the data was normally distributed. Shapiro-Wilk test for the data was not significant ($p = 0.099$), suggesting that the data was normally distributed. There appeared to be only one mode/peak in the data, thus making it unimodal.

Since majority of the 3 criteria (skewness, kurtosis, Shapiro-Wilk test) were suggestive of normality, it appeared that the data was normally distributed (approximately followed a bell-shaped curve).

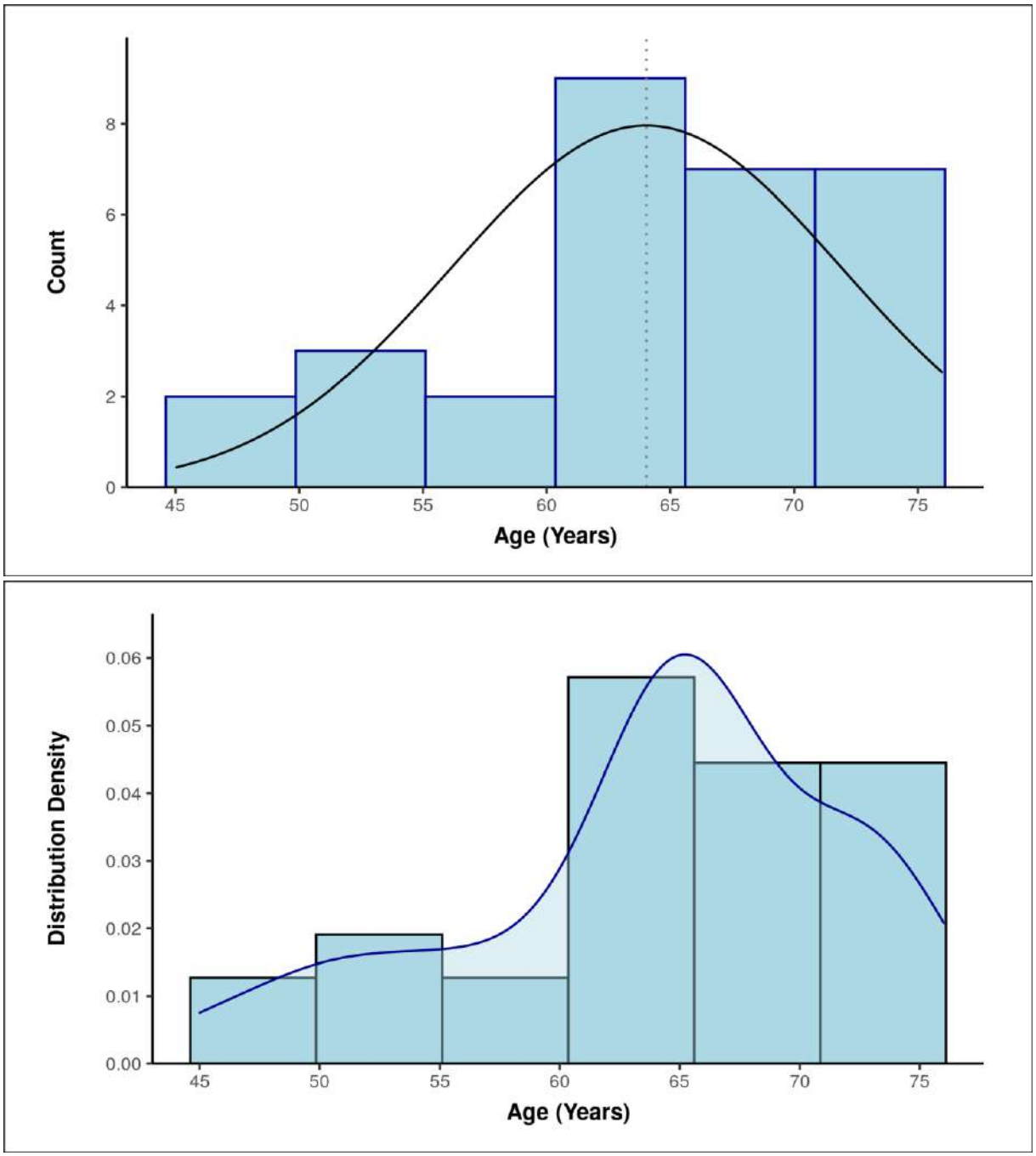


Figure 5a and 5b: The following histogram is plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference: Distribution of Participants in terms of Age (Years)

Distribution of the Participants in Terms of Initial PSA

PSA (ng/mL) (Initial)	
Mean (SD)	45.00 (42.45)
Median (IQR)	29.5 (20.25-50.75)
Range	6 - 203

The mean (SD) of PSA (ng/mL) (Initial) was 45.00 (42.45). The median (IQR) of PSA (ng/mL) (Initial) was 29.50 (20.25-50.75). The PSA (ng/mL) (Initial) ranged from 6 - 203.

The skewness of the data was 2.1, and it suggested that the data was positively skewed, thus suggesting it was not normally distributed. The kurtosis of the data was 4.54, and it suggested that the data was not normally distributed. Shapiro-Wilk test for the data was significant ($p = <0.001$), suggesting that the data was not normally distributed. There appeared to be only one mode/peak in the data, thus making it unimodal.

Since none of the 3 criteria (skewness, kurtosis, Shapiro-Wilk test) were suggestive of normality, it appeared that the data was not normally distributed (did not follow a bell-shaped curve).

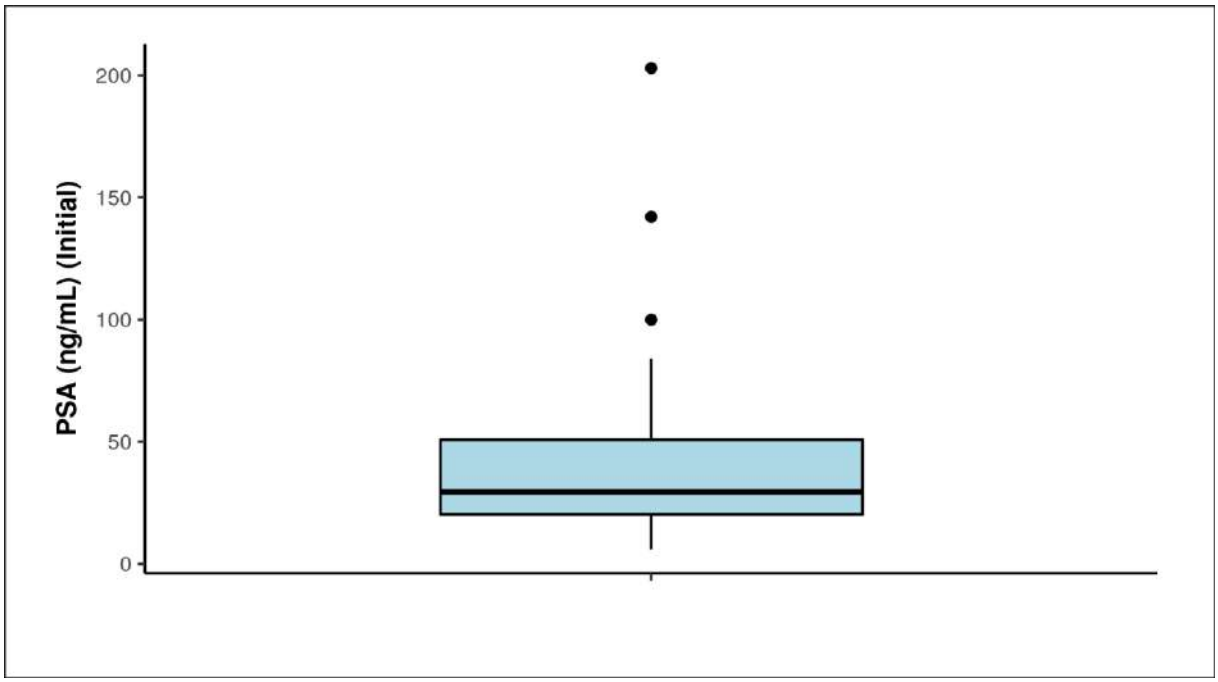
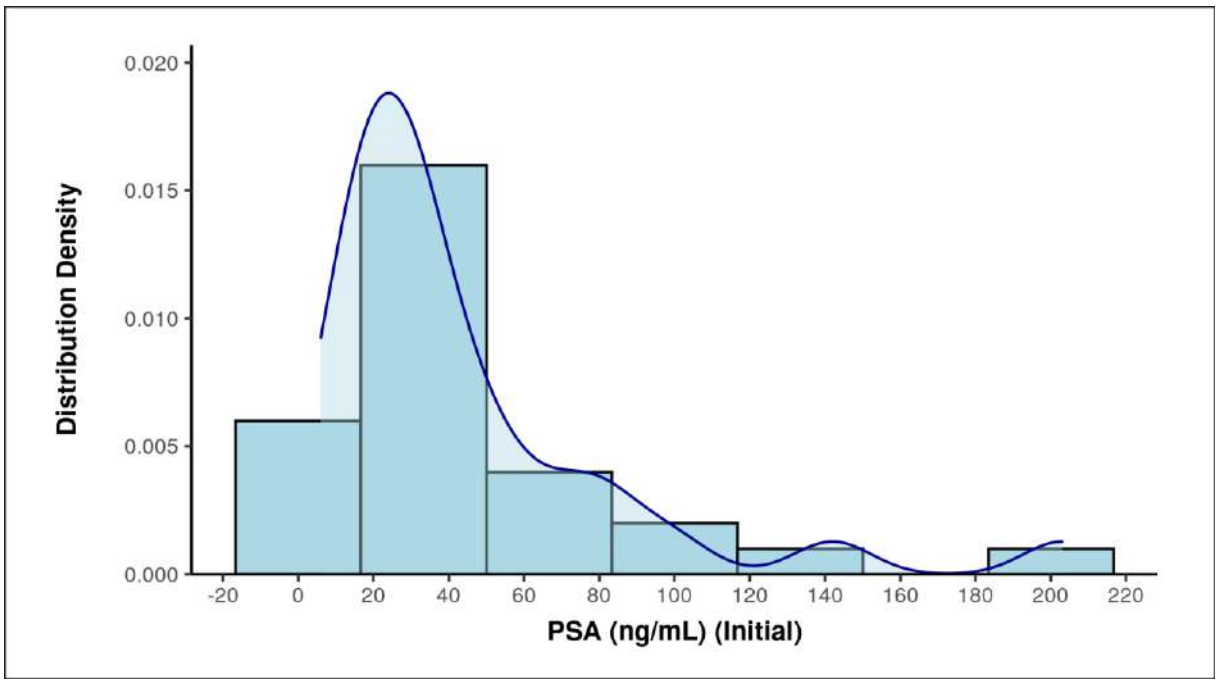


Figure 6a: Distribution of Participants in terms of Initial PSA (ng/mL)



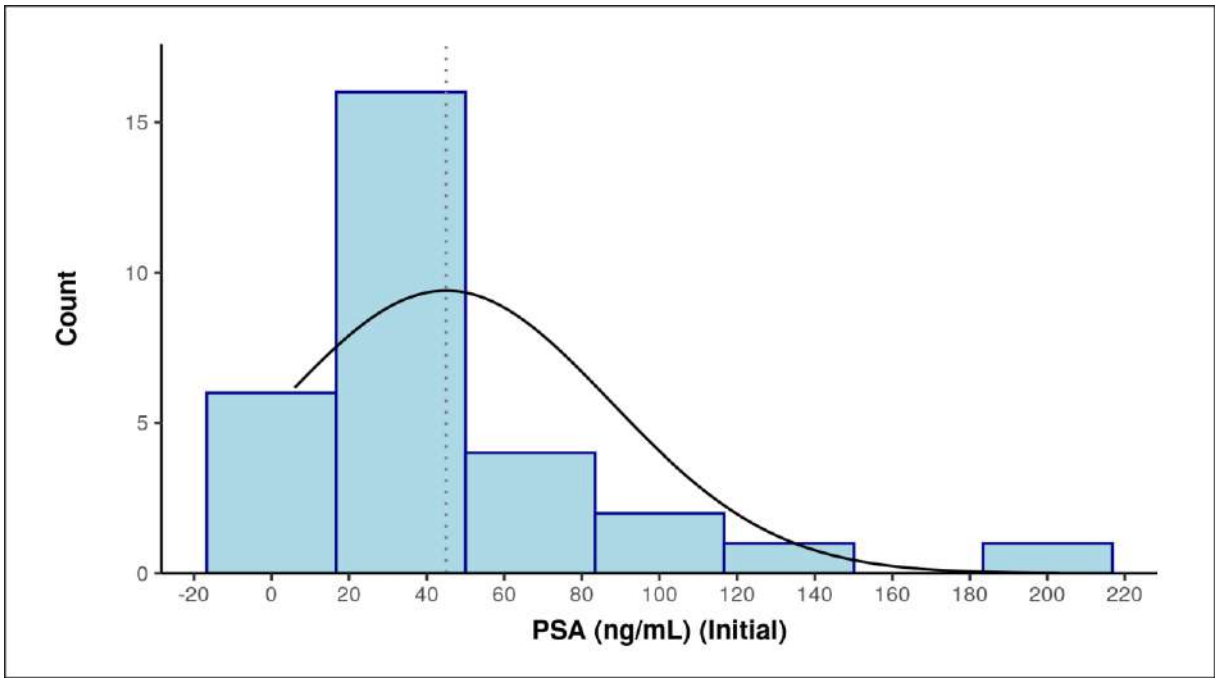


Figure 6b and 6c: The following histogram in plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference.Distribution of Participants in terms of Initial PSA (ng/mL)

Distribution of the Participants in Terms of PIRADS score

PIRADS score	Frequency	Percentage	95% CI
PIRADS 3	2	7.1%	1.2% - 25.0%
PIRADS 4	4	14.3%	4.7% - 33.6%
PIRADS 5	22	78.6%	58.5% - 91.0%

7.1% of the participants had PIRADS score of 3.

14.3% of the participants had PIRADS score: PIRADS 4.

78.6% of the participants had PIRADS score: PIRADS 5.

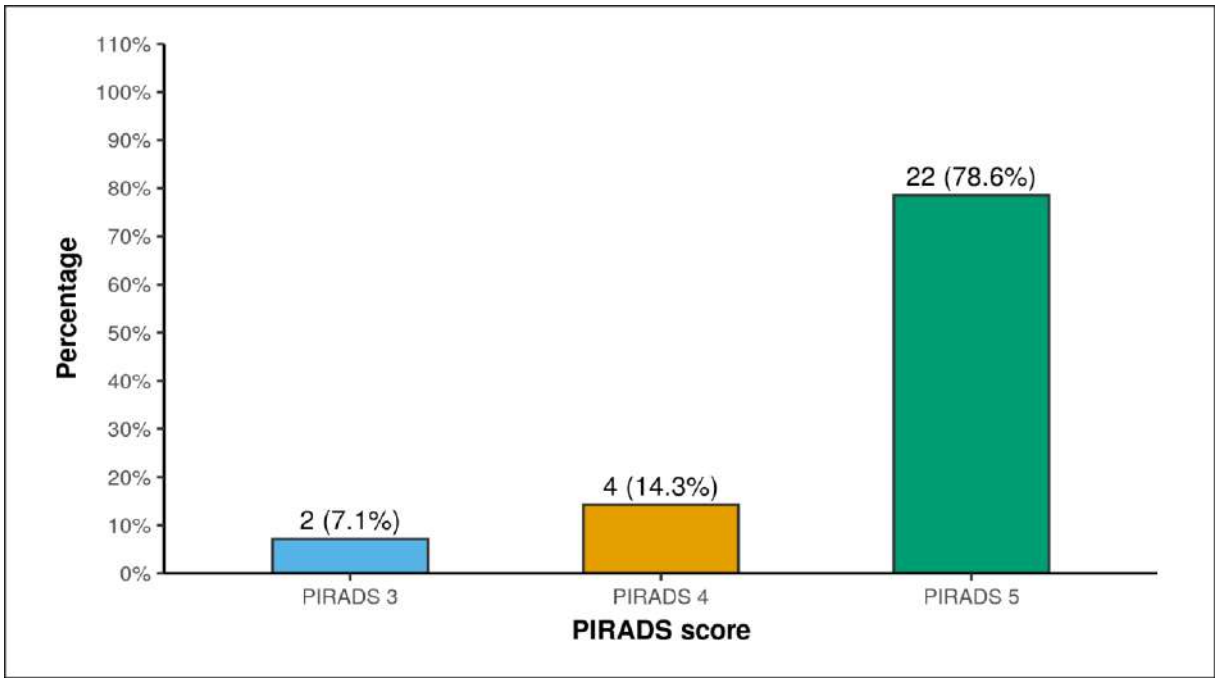


Figure 7: Distribution of Participants in terms of PIRADS Score

Distribution of the Participants in Terms of ISUP Grade Group

ISUP	Frequency	Percentage	95% CI
Grade 1	4	13.3%	4.4% - 31.6%
Grade 2	3	10.0%	2.6% - 27.7%
Grade 3	9	30.0%	15.4% - 49.6%
Grade 4	7	23.3%	10.6% - 42.7%
Grade 5	7	23.3%	10.6% - 42.7%

13.3% of the participants had ISUP: Grade 1.

10.0% of the participants had ISUP: Grade 2.

30.0% of the participants had ISUP: Grade 3.

23.3% of the participants had ISUP: Grade 4.

23.3% of the participants had ISUP: Grade 5.

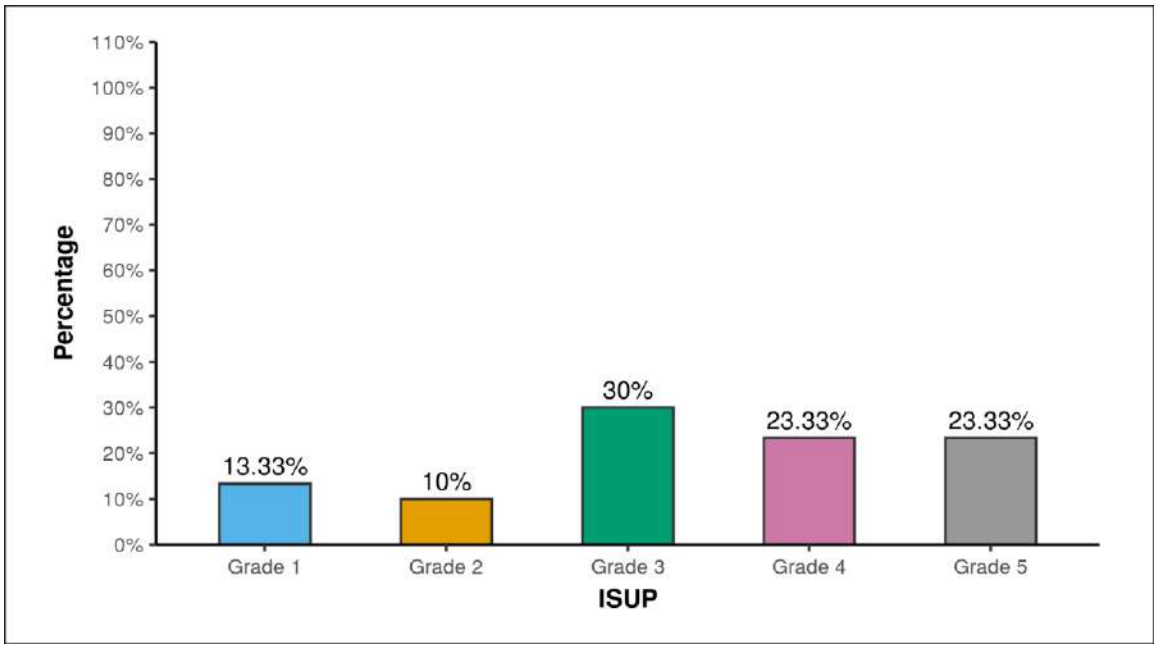


Figure 8: Distribution of Participants in terms of ISUP

Distribution of the Participants in Terms of Clinical T Stage(cT)

T Stage (Clinical)	Frequency	Percentage	95% CI
T2	8	26.7%	13.0% - 46.2%
T3a	8	26.7%	13.0% - 46.2%
T3b	11	36.7%	20.5% - 56.1%
T4	3	10 %	2.6% - 27.7%

26.7% of the participants had T Stage (Clinical): T2.

26.7% of the participants had T Stage (Clinical): T3a.

36.7% of the participants had T Stage (Clinical): T3b.

10.0% of the participants had T Stage (Clinical): T4.

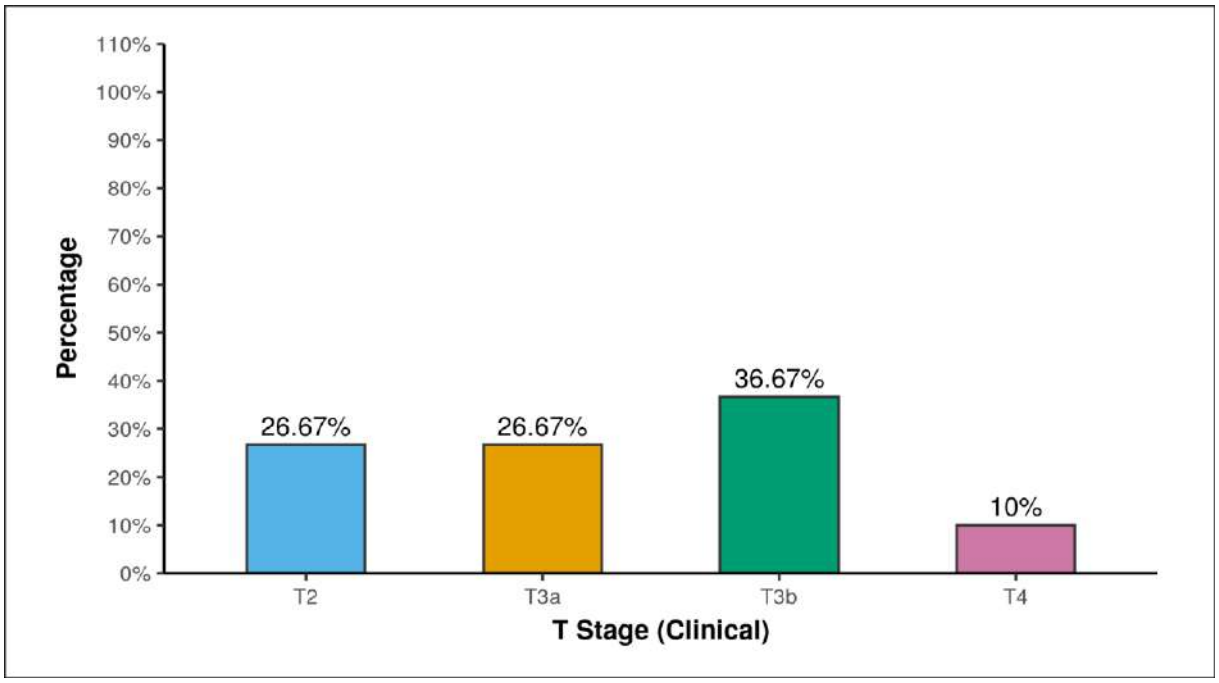


Figure 9: Distribution of participants in terms of clinical T Stage

Distribution of the Participants in Terms of Pathological T Stage (pT)

T Stage (Pathological)	Frequency	Percentage	95% CI
T2	8	26.7%	13.0% - 46.2%
T3a	3	10.0%	2.6% - 27.7%
T3b	17	56.7%	37.7% - 74.0%
T4	2	6.7%	1.2% - 23.5%

26.7% of the participants had T Stage (Pathological): T2.

10.0% of the participants had T Stage (Pathological): T3a.

56.7% of the participants had T Stage (Pathological): T3b.

6.7% of the participants had T Stage (Pathological): T4.

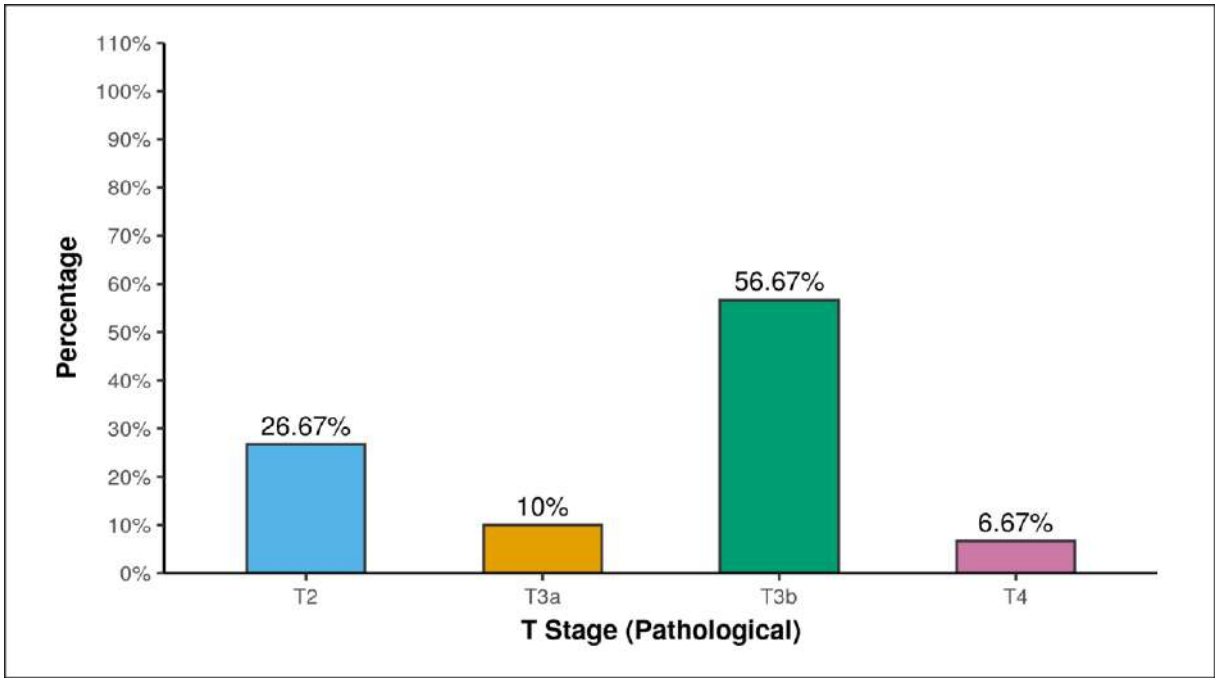


Figure 10: Distribution of participants in terms of pathological T Stage

Distribution of the Participants in Terms of Preoperative N stage

N Stage (Clinical)	Frequency	Percentage	95% CI
N0	21	70.0%	50.4% - 84.6%
N1	9	30.0%	15.4% - 49.6%

70.0% of the participants had N Stage (Clinical): N0. 30.0% of the participants had N Stage (Clinical): N1.

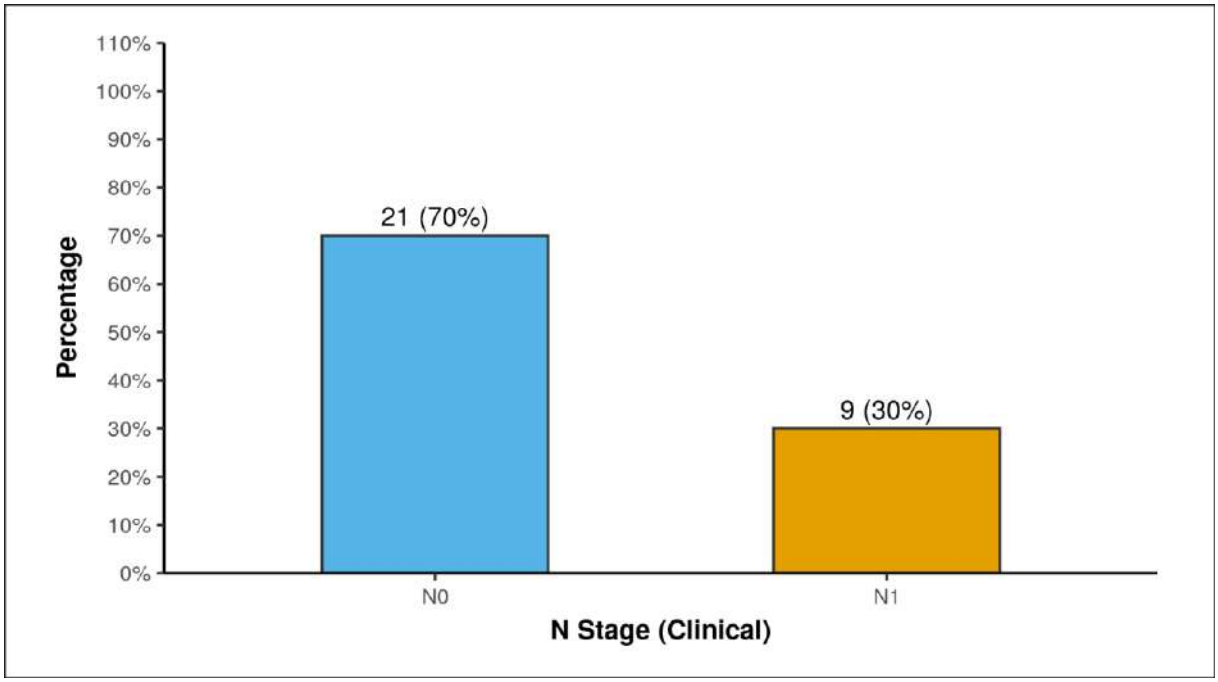


Figure 11: Distribution of Participants in terms of preoperative N Stage (Clinical)

Distribution of the Participants in Terms of M Stage

M Stage	Frequency	Percentage	95% CI
M0	20	66.7%	47.1% - 82.1%
M1b	10	33.3%	17.9% - 52.9%

66.7% of the participants had M Stage: M0. 33.3% of the participants had M Stage: M1b.

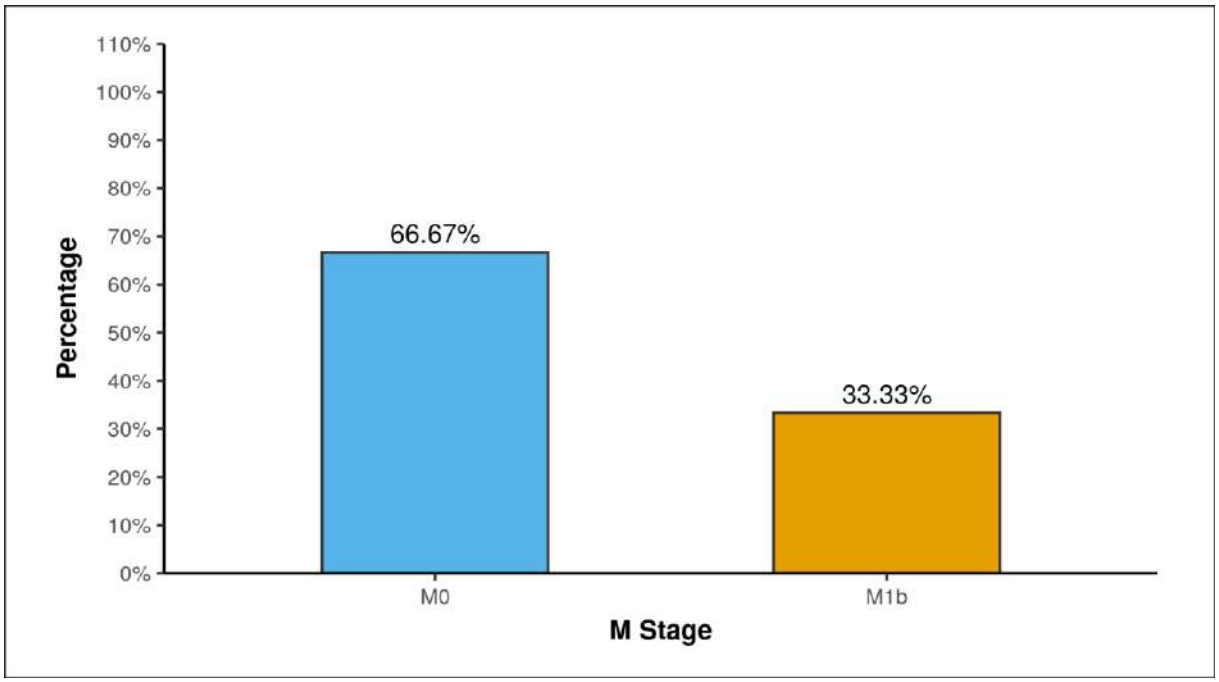


Figure 12: Distribution of participants in terms of M Stage

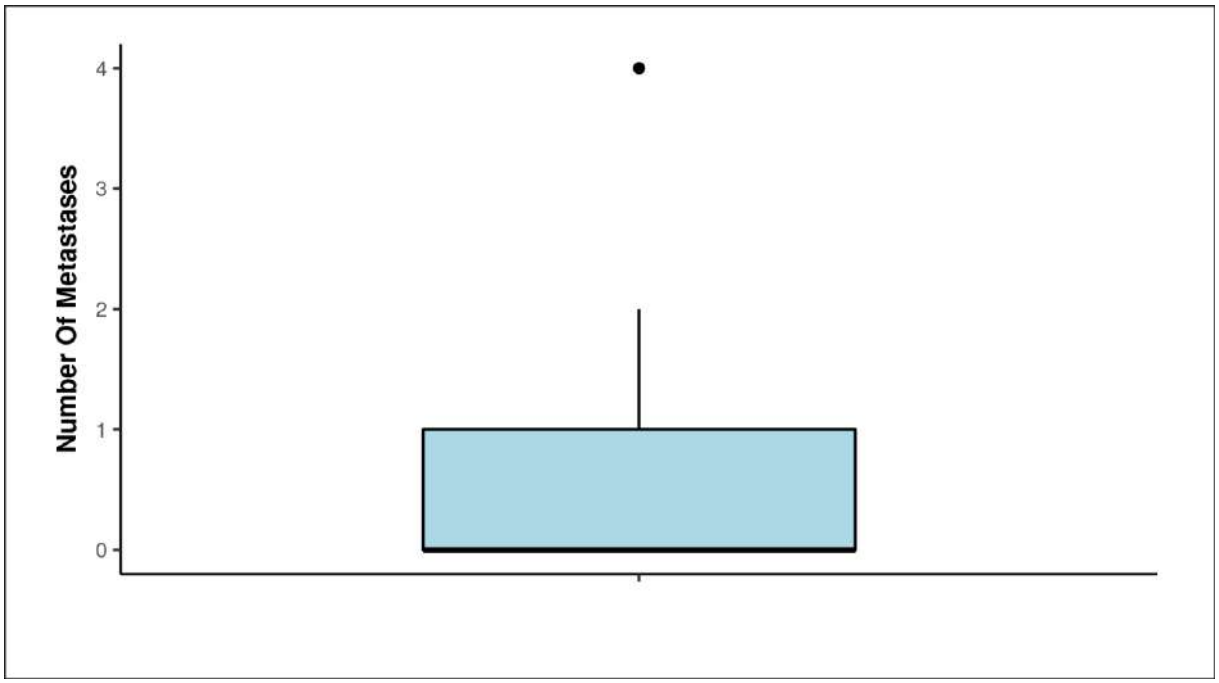
Distribution of the Participants in Terms of Number Of Osseous Metastases

Number Of Metastases	
Mean (SD)	0.47 (0.86)
Median (IQR)	0 (0-1)
Range	0 - 4

The mean (SD) of Number Of Metastases was 0.47 (0.86). The median (IQR) of Number Of Metastases was 0.00 (0-1). The Number Of Metastases ranged from 0 - 4.

The skewness of the data was 2.45, and it suggested that the data was positively skewed, thus suggesting it was not normally distributed. The kurtosis of the data was 6.92, and it suggested that the data was not normally distributed. Shapiro-Wilk test for the data was significant (p = <0.001), suggesting that the data was not normally distributed. There appeared to be more than one mode/peak in the data, thus making it multimodal.

Since the data was multimodal (had more than one peak), it appeared that the data was not normally distributed (did not follow a bell-shaped curve).



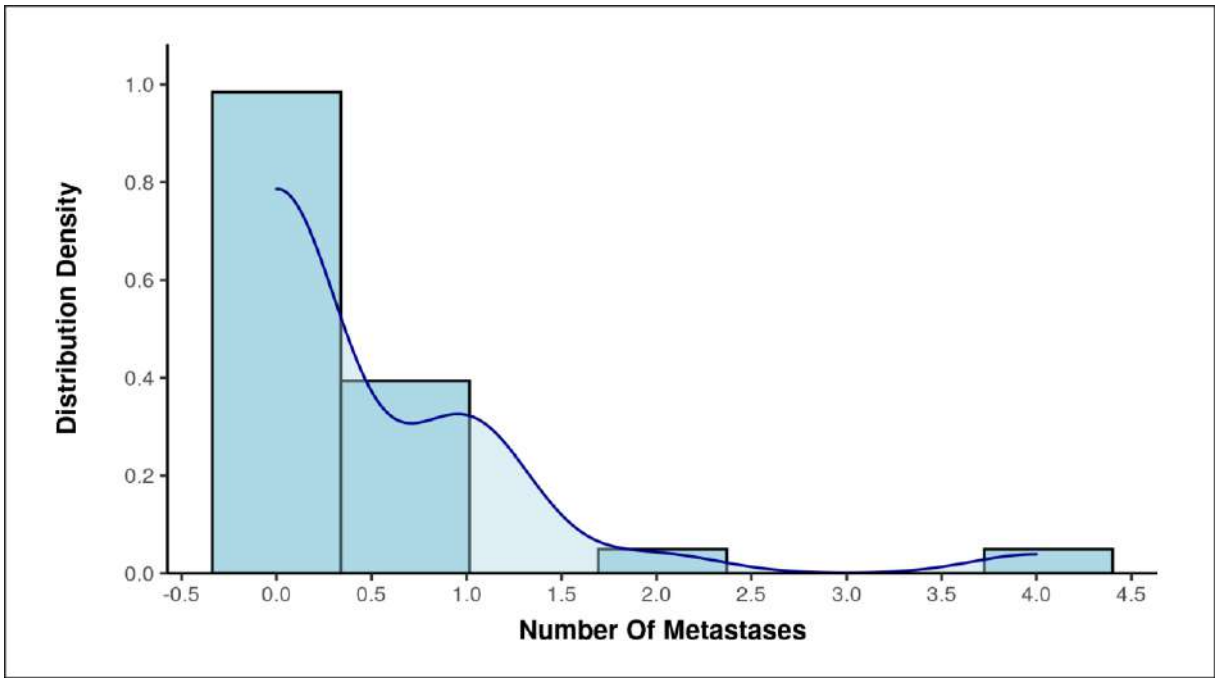


Figure 13a and 13b: The following histogram in plotted with the actual counts, and an ideal bell-shaped curve is superimposed on top for reference: Distribution of participants in terms of Number of Osseous Metastases

Table 7: SUMMARY OF ALL DESCRIPTIVE PARAMETERS

All Parameters	Mean ± SD || Median (IQR) || Min-Max OR N (%)
Management	
Radical Prostatectomy	22 (73.3%)
Radiotherapy	8 (26.7%)
Age (Years)	64.03 ± 7.89 || 65.00 (61.25-69.50) || 45.00 - 76.00
Age	
40-49 Years	2 (6.7%)
50-59 Years	5 (16.7%)
60-69 Years	15 (50.0%)
70-79 Years	8 (26.7%)
PSA (ng/mL) (Initial)	45.00 ± 42.45 || 29.50 (20.25-50.75) || 6.00 - 203.00
PSA (ng/mL) (3 Months)	0.40 ± 1.02 || 0.07 (0.02-0.21) || 0.00 - 5.26
PIRADS score	
PIRADS 3	2 (7.1%)
PIRADS 4	4 (14.3%)
PIRADS 5	22 (78.6%)

All Parameters	Mean ± SD || Median (IQR) || Min-Max OR N (%)
ISUP	
Grade 1	4 (13.3%)
Grade 2	3 (10.0%)
Grade 3	9 (30.0%)
Grade 4	7 (23.3%)
Grade 5	7 (23.3%)
T Stage (Clinical)	
T2	8 (26.7%)
T3a	8 (26.7%)
T3b	11 (36.7%)
T4	3 (10.0%)
T Stage (Pathological)	
T2	8 (26.7%)
T3a	3 (10.0%)
T3b	17 (56.7%)
T4	2 (6.7%)
N Stage (Clinical)	
N0	21 (70.0%)
N1	9 (30.0%)
N Stage (Pathological)	
N0	18 (60.0%)
N1	12 (40.0%)
M Stage	
M0	20 (66.7%)
M1b	10 (33.3%)
Number Of Metastases	0.47 ± 0.86 || 0.00 (0.00-1.00) || 0.00 - 4.00
LVI (Yes)	3 (10.0%)
PNI (Yes)	24 (80.0%)

Of the participants, 22 (73.3%) underwent radical prostatectomy as their primary form of management, while 8 (26.7%) received radiotherapy. The average age of the participants was 64.03 ± 7.89 years. Specifically, 2 (6.7%) fell within the 40-49 year range, 5 (16.7%) were aged between 50-59 years, 15 (50.0%) were between 60-69 years, and 8 (26.7%) were in the 70-79 year bracket. The mean initial PSA level was 45.00 ± 42.45 ng/mL, and this decreased significantly to 0.40 ± 1.02 ng/mL after three months. In terms of PIRADS scores, 2 (7.1%) had a PIRADS score of 3, 4 (14.3%) had a PIRADS score of 4, and the majority, 22 (78.6%), had a PIRADS score of 5. Regarding ISUP grades, 4 (13.3%) were

graded as ISUP 1, 3 (10.0%) as ISUP 2, 9 (30.0%) as ISUP 3, and 7 (23.3%) each were graded as ISUP 4 and ISUP 5.

Clinical T stage classification revealed that 8 (26.7%) of the participants were categorized as T2, 8 (26.7%) as T3a, 11 (36.7%) as T3b, and 3 (10.0%) as T4. Pathological T stage results indicated that 8 (26.7%) were T2, 3 (10.0%) were T3a, 17 (56.7%) were T3b, and 2 (6.7%) were T4. For the clinical N stage, 21 (70.0%) of the participants were classified as N0, while 9 (30.0%) were N1. Similarly, pathological N stage demonstrated that 18 (60.0%) were N0, and 12 (40.0%) were N1. In terms of metastasis (M stage), 20 (66.7%) of the participants were categorized as M0, while 10 (33.3%) were M1b. The average number of metastases was 0.47 ± 0.86. Lymphovascular invasion (LVI) was observed in 3 (10.0%) of the participants, with 27 (90.0%) showing no signs of LVI. Perineural invasion (PNI) was present in 24 (80.0%) of the participants, while 6 (20.0%) did not exhibit PNI.

ASSOCIATION BETWEEN RLT AND PARAMETERS

Association between type of RLT and Age

Age (Years)	Management		Wilcoxon-Mann-Whitney U Test	
	Radical Prostatectomy	Radiotherapy	W	p value
Mean (SD)	62.73 (7.92)	67.62 (7.07)	52.000	0.095
Median (IQR)	64.5 (58.75-66.75)	69 (64.75-73.25)		
Min - Max	45 - 76	53 - 74		

The variable Age (Years) was not normally distributed in the 2 subgroups of the variable Management. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of Age (Years) in the Management: Radical Prostatectomy group was 62.73 (7.92).

The mean (SD) of Age (Years) in the Management: Radiotherapy group was 67.62 (7.07).

The median (IQR) of Age (Years) in the Management: Radical Prostatectomy group was 64.5 (58.75-66.75).

The median (IQR) of Age (Years) in the Management: Radiotherapy group was 69 (64.75-73.25). The Age (Years) in the two radical local therapy subgroups ranged from 45 - 76 and. 53 – 74 respectively.

There was no significant difference between the groups in terms of Age (Years) (W = 52.000, p = 0.095).

Strength of Association (Point-Biserial Correlation) = 0.28 (Medium Effect Size)

The Box-and-Whisker plot below depicts the distribution of Age (Years) in the 2 groups. The middle horizontal line represents the median Age (Years), the upper and lower bounds of the box represent the 75th and the 25th centile of Age (Years) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Age (Years) in each of the groups.

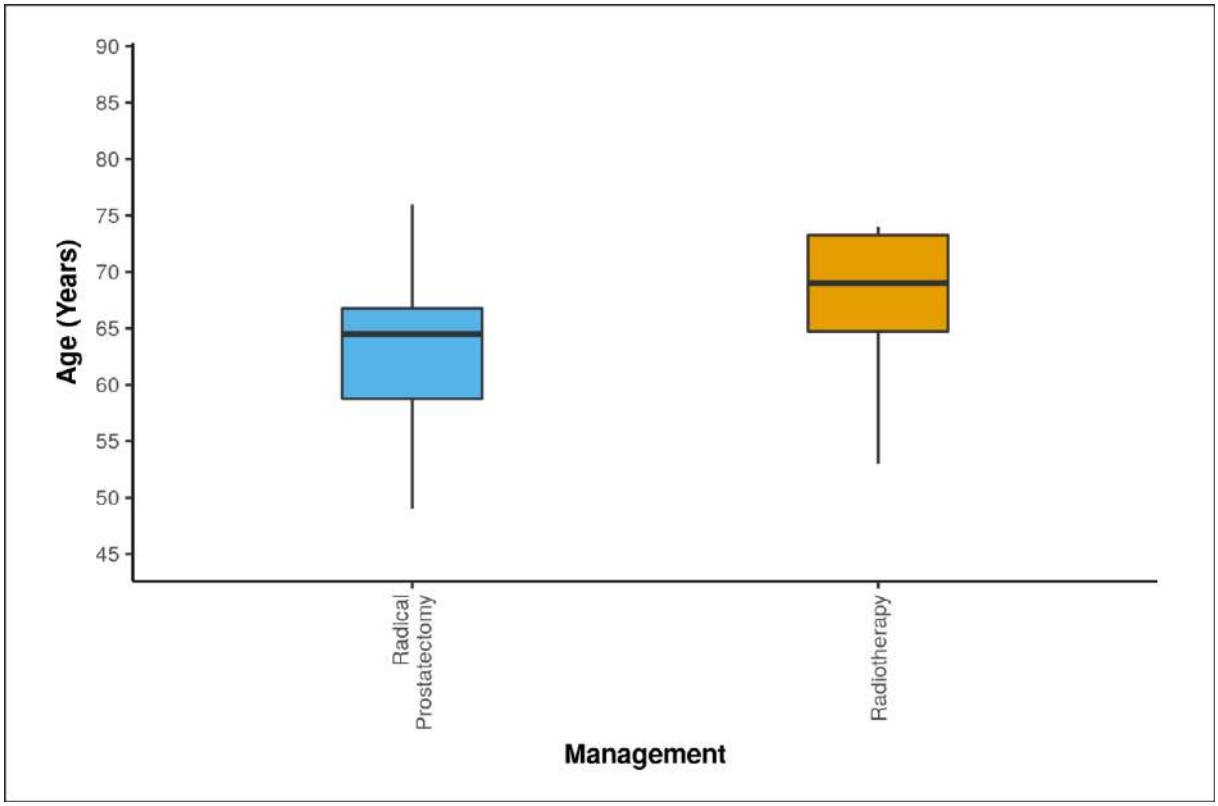


Figure 14a-14b: Association Between Type of RLT and Age (Years)

Association between type of RLT and Initial PSA (ng/mL)

PSA (ng/mL) (Initial)	Management		Wilcoxon-Mann-Whitney U Test	
	Radical Prostatectomy	Radiotherapy	W	p value
Mean (SD)	39.68 (32.96)	59.62 (62.24)	70.000	0.412
Median (IQR)	28.5 (16.5-48.75)	33.5 (23-66.75)		
Min - Max	6 - 142	18 - 203		

The variable initial PSA (ng/mL) was not normally distributed in the 2 subgroups of the variable RLT. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of initial PSA (ng/mL) in the RLT group: Radical Prostatectomy was 39.68

.

The mean (SD) of initial PSA (ng/mL) in the RLT group: Radiotherapy was 59.62.

The median (IQR) of initial PSA (ng/mL) in the RLT group: Radical Prostatectomy was 28.5 (16.5-48.75).

The median (IQR) of initial PSA (ng/mL) in the RLT group: Radiotherapy was 33.5 (23-66.75). The initial PSA (ng/mL) in the RP group ranged from 6 - 142. The initial PSA (ng/mL) in the RLT group: Radiotherapy ranged from 18 - 203.

There was no significant difference between the groups in terms of initial PSA (ng/mL) (Initial) (W = 70.000, p = 0.412).

The Box-and-Whisker plot below depicts the distribution of PSA (ng/mL) (Initial) in the 2 groups. The middle horizontal line represents the median PSA (ng/mL) (Initial), the upper and lower bounds of the box represent the 75th and the 25th centile of PSA (ng/mL) (Initial) respectively, and the upper and lower extent of the whiskers represent the Tukey limits for PSA (ng/mL) (Initial) in each of the groups.

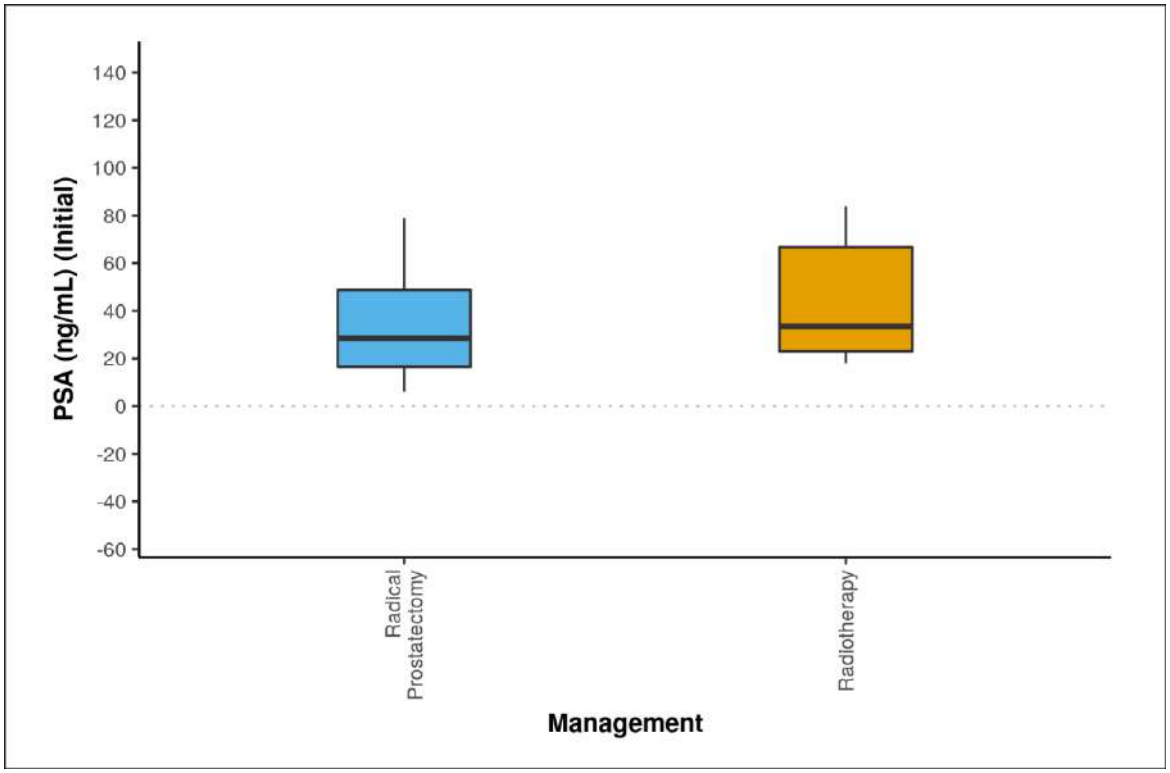


Figure 15: Association Between type of RLT and Initial PSA (ng/mL)

Association between type of RLT and PSA (ng/mL) at 3 Months

PSA (ng/mL) (3 Months)	Management		Wilcoxon-Mann-Whitney U Test	
	Radical Prostatectomy	Radiotherapy	W	p value
Mean (SD)	0.50 (1.18)	0.10 (0.10)	98.500	0.639
Median (IQR)	0.07 (0.02-0.32)	0.09 (0.01-0.17)		
Min - Max	0 - 5.26	0 - 0.25		

The variable PSA (ng/mL) at 3 months post RLT was not normally distributed in the 2 subgroups of the variable Management. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of PSA (ng/mL) at 3 months (3 Months) in the RLT: Radical Prostatectomy group was 0.50 (1.18). The mean (SD) of PSA (ng/mL) at 3 months in the RLT: Radiotherapy group was 0.10 (0.10). The median (IQR) of PSA (ng/mL) at 3 Months in the RLT: Radical Prostatectomy group was 0.07 (0.02-0.32). The median (IQR) of PSA (ng/mL) at 3 Months in the RLT: Radiotherapy group was 0.09 (0.01-0.17). The PSA (ng/mL) at 3 Months in the RLT: Radical Prostatectomy ranged from 0 - 5.26. The PSA (ng/mL) at 3 Months in the RLT: Radiotherapy ranged from 0 - 0.25.

There was no significant difference between the groups in terms of PSA (ng/mL) at 3 Months ($W = 98.500$, $p = 0.639$).

Strength of Association (Point-Biserial Correlation) = 0.18 (Small Effect Size)

The Box-and-Whisker plot below depicts the distribution of PSA (ng/mL) at 3 Months in the 2 groups. The middle horizontal line represents the median PSA (ng/mL) at 3 Months, the upper and lower bounds of the box represent the 75th and the 25th centile of PSA

(ng/mL) at 3 Months respectively, and the upper and lower extent of the whiskers represent the Tukey limits for PSA (ng/mL) at 3 Months in each of the groups.

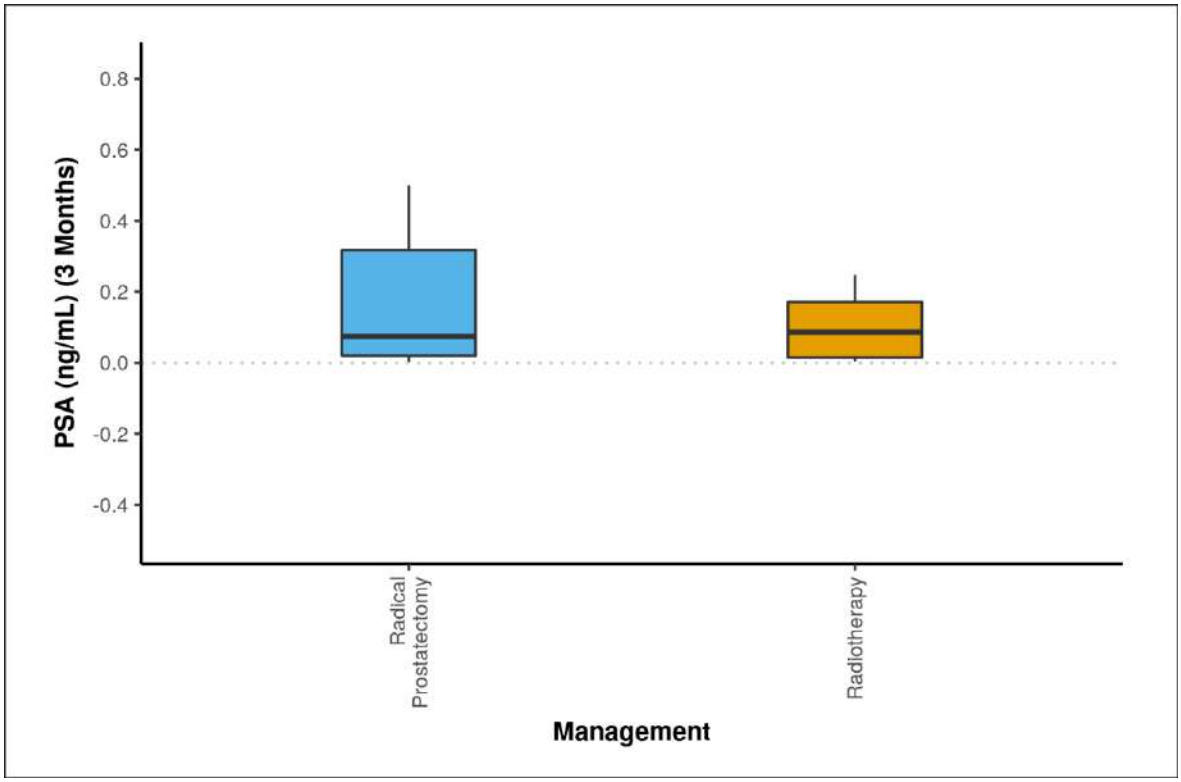


Figure 16a: Association Between type of RLT and PSA (ng/mL) at 3 Months

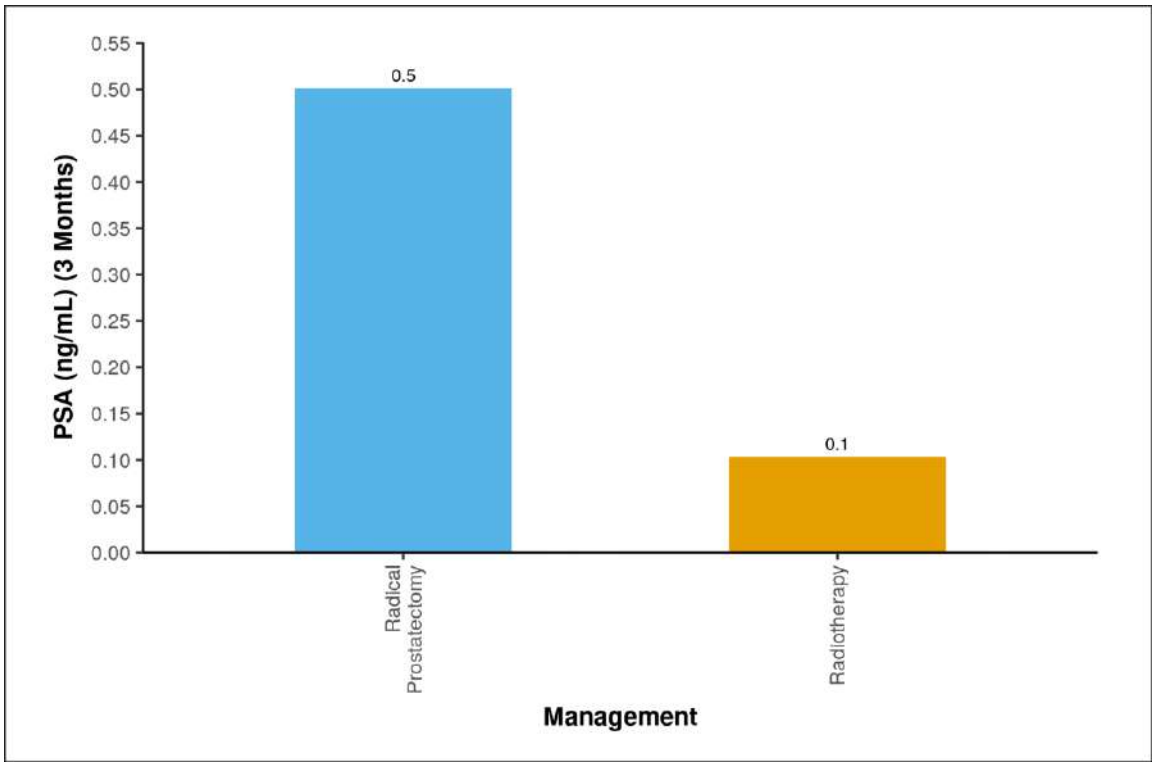


Figure 16b: Association Between type of RLT and PSA (ng/mL)at 3 Months

Association between type of RLT and Change in PSA (ng/mL) at 3 Months

Change in PSA (ng/mL) (3 Months)	Management		Wilcoxon-Mann-Whitney U Test	
	Radical Prostatectomy	Radiotherapy	W	p value
Mean (SD)	-39.18 (33.10)	-59.52 (62.27)	108.000	0.368
Median (IQR)	-28.45 (-48.62--16.21)	-33.43 (-66.67--22.88)		
Min - Max	-141.93 - -5.88	-202.98 - -17.75		

The variable Change in PSA at 3 months ng/mL was not normally distributed in the 2 subgroups of the variable RLT. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the RLT: Radical Prostatectomy group was -39.18 (33.10).

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the RLT: Radiotherapy group was -59.52 (62.27).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the RLT: Radical Prostatectomy group was -28.45 (-48.62--16.21).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the RLT: Radiotherapy group was -33.43 (-66.67--22.88).

The Change in PSA (ng/mL) at 3 Months in the RLT: Radical Prostatectomy ranged from -141.93 - -5.88.

The Change in PSA (ng/mL) at 3 Months in the RLT: Radiotherapy ranged from -202.98 - -17.75.

There was no significant difference between the groups in terms of Change in PSA (ng/mL) at 3 Months (W = 108.000, p = 0.368).

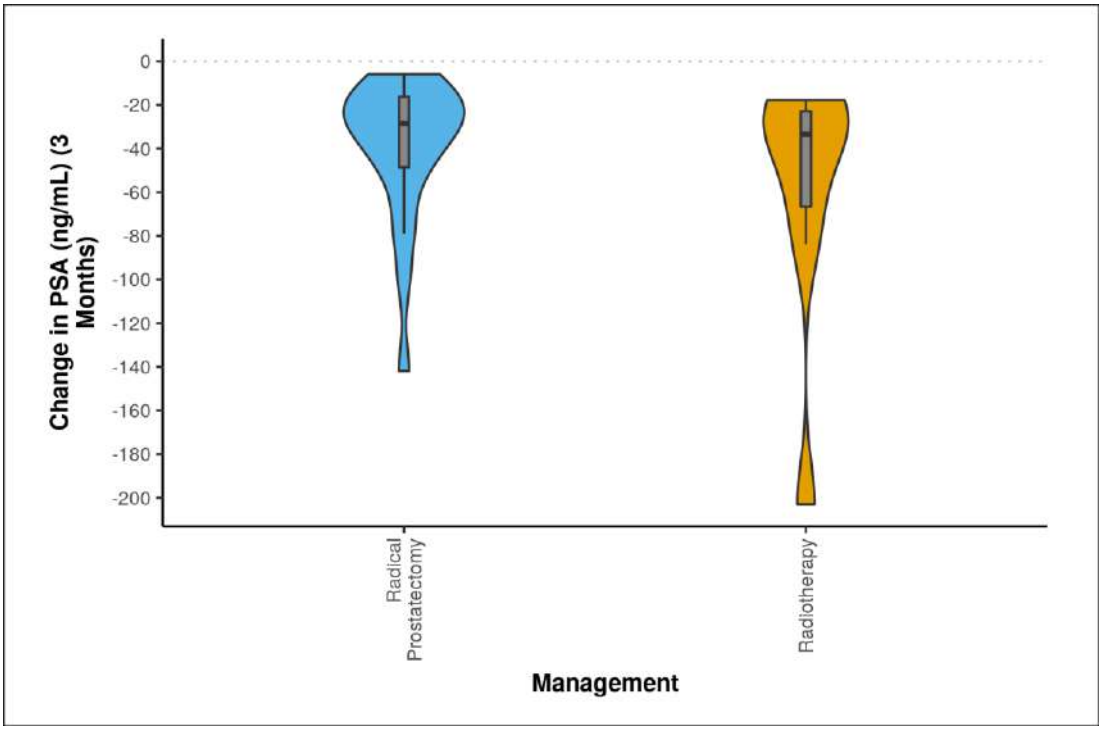


Figure 17a: Association Between RLT and Change in PSA (ng/mL) at 3 Months (Box Whisker plot)

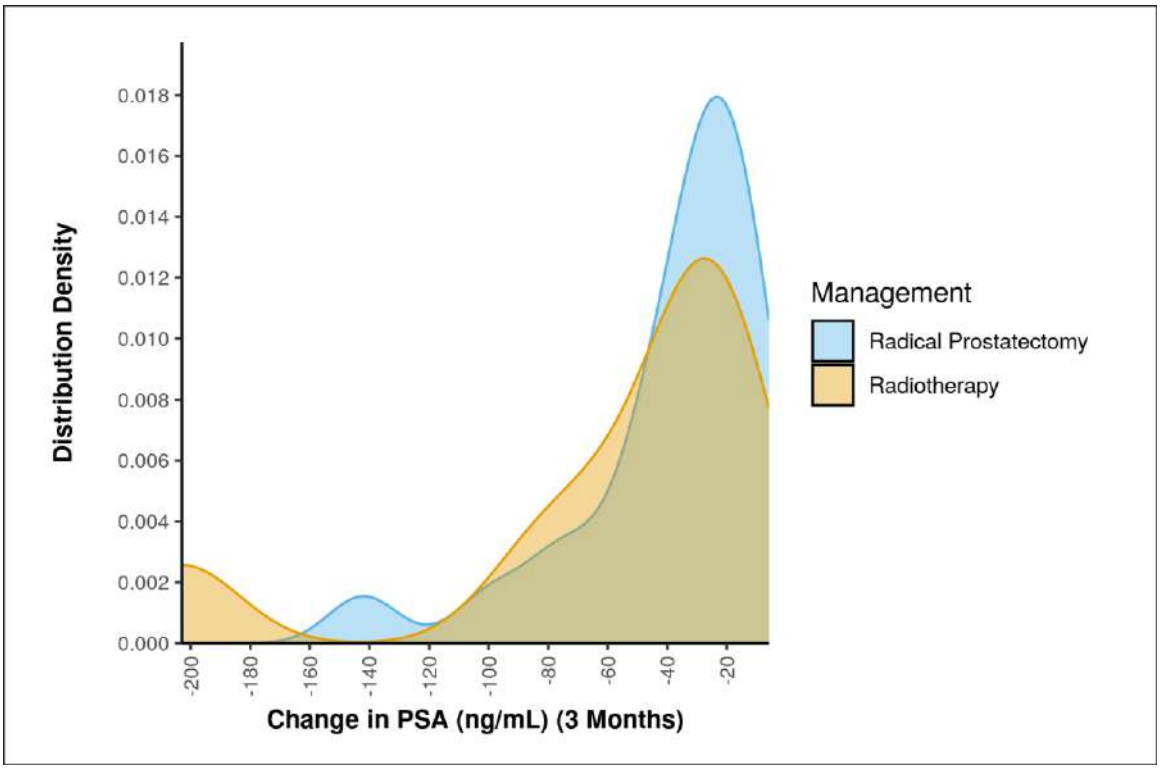


Figure 17b: Association Between RLT and Change in PSA (ng/mL) at 3 Months (Density plot)

Association Between type of RLT and PIRADS score

PIRADS score	Management			Fisher's Exact Test	
	Radical Prostatectomy	Radiotherapy	Total	$\chi 2$	P Value
PIRADS 3	2 (10.0%)	0 (0.0%)	2 (7.1%)	3.055	0.335
PIRADS 4	4 (20.0%)	0 (0.0%)	4 (14.3%)		
PIRADS 5	14 (70.0%)	8 (100.0%)	22 (78.6%)		
Total	20 (100.0%)	8 (100.0%)	28 (100.0%)		

PIRADS score	Adjusted P Values
PIRADS 3 vs. PIRADS 4	1.000
PIRADS 3 vs. PIRADS 5	0.804
PIRADS 4 vs. PIRADS 5	0.804

Fisher's exact test was used to explore the association between type of RLT and PIRADS score as more than 20% of the total number of cells had an expected count of less than 5.

There was no significant difference between the various groups in terms of distribution of PIRADS score ($\chi 2 = 3.055$, $p = 0.335$).

Strength of association between the two variables (Cramer's V) = 0.33 (Moderate Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.19 (Low Association)

10.0% of the participants in the group RLT: RP had [PIRADS score: PIRADS 3].

20.0% of the participants in the group RLT: RP had [PIRADS score: PIRADS 4].

70.0% of the participants in the RLT group: RP had [PIRADS score: PIRADS 5].

100.0% of the participants in the RLT group: RT had [PIRADS score: PIRADS 5].

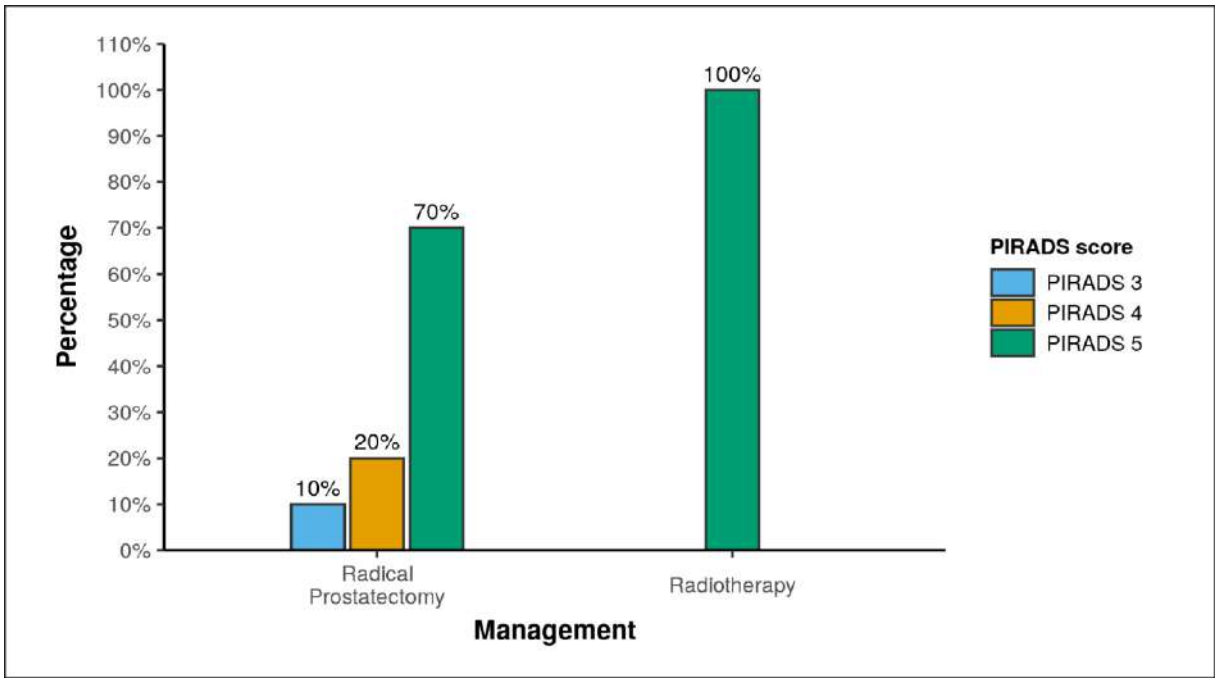


Figure 18a: Association between RLT and PIRADS score

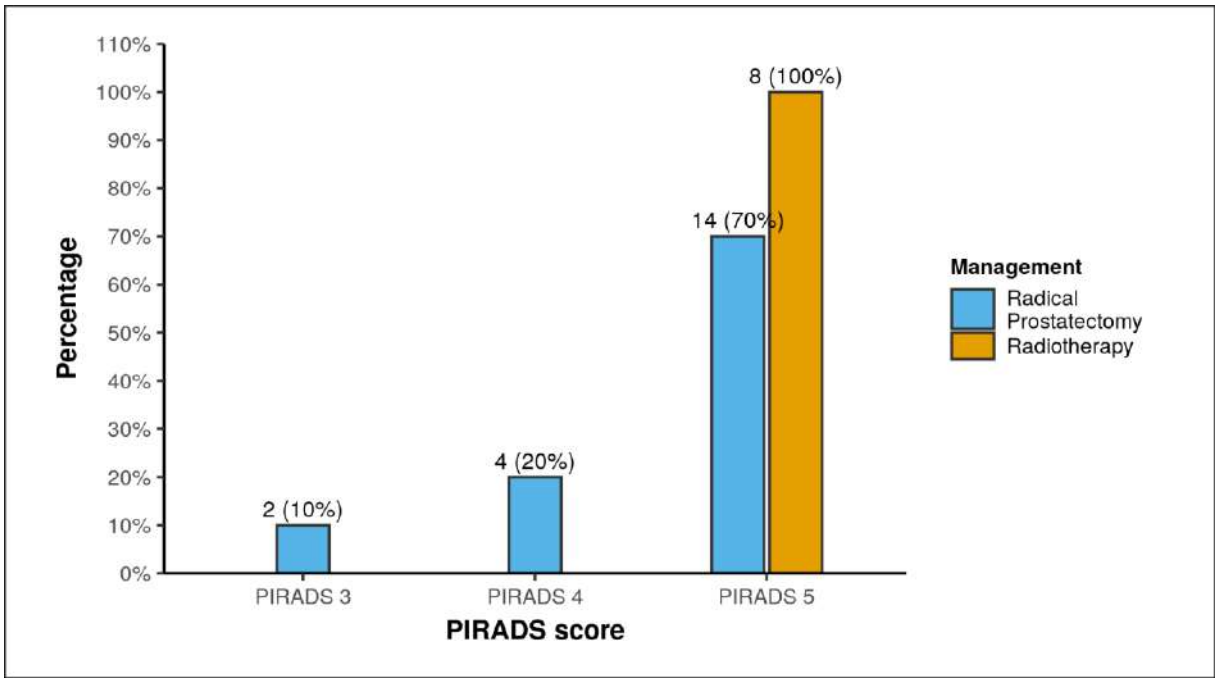


Figure 18b: Association between RLT and PIRADS score

(Two patients underwent MRI post biopsy, hence PIRADS score was not applicable) *

Association Between RLT and ISUP

ISUP	Management			Fisher's Exact Test	
	Radical Prostatectomy	Radiotherapy	Total	$\chi 2$	P Value
Grade 1	3 (13.6%)	1 (12.5%)	4 (13.3%)	2.788	0.751
Grade 2	3 (13.6%)	0 (0.0%)	3 (10.0%)		
Grade 3	6 (27.3%)	3 (37.5%)	9 (30.0%)		
Grade 4	6 (27.3%)	1 (12.5%)	7 (23.3%)		
Grade 5	4 (18.2%)	3 (37.5%)	7 (23.3%)		
Total	22 (100.0%)	8 (100.0%)	30 (100.0%)		

Fisher's exact test was used to explore the association between type of RLT' and 'ISUP' as more than 20% of the total number of cells had an expected count of less than 5.

There was no significant difference between the various groups in terms of distribution of ISUP ($\chi 2 = 2.788$, $p = 0.751$).

Strength of association between the two variables (Cramer's V) = 0.3 (Low Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0 (Little/No Association)

13.6% of the participants in the group [RLT: Radical Prostatectomy] had [ISUP: Grade 1].

13.6% of the participants in the group [RLT: Radical Prostatectomy] had [ISUP: Grade 2].

27.3% of the participants in the group [RLT: Radical Prostatectomy] had [ISUP: Grade 3].

27.3% of the participants in the group [RLT: Radical Prostatectomy] had [ISUP: Grade 4].

18.2% of the participants in the group [RLT: Radical Prostatectomy] had [ISUP: Grade 5].

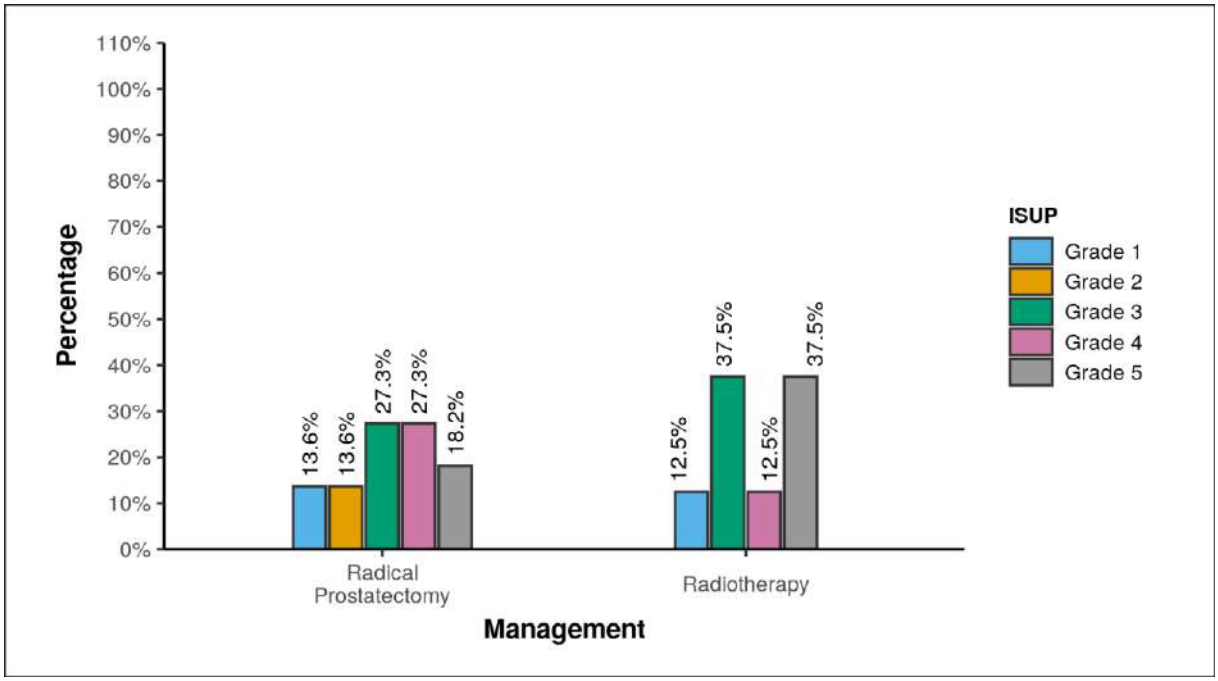
12.5% of the participants in the group [RLT: Radiotherapy] had [ISUP: Grade 1].

0.0% of the participants in the group [RLT: Radiotherapy] had [ISUP: Grade 2].

37.5% of the participants in the group [RLT: Radiotherapy] had [ISUP: Grade 3].

12.5% of the participants in the group [RLT: Radiotherapy] had [ISUP: Grade 4].

37.5% of the participants in the group [RLT: Radiotherapy] had [ISUP: Grade 5].



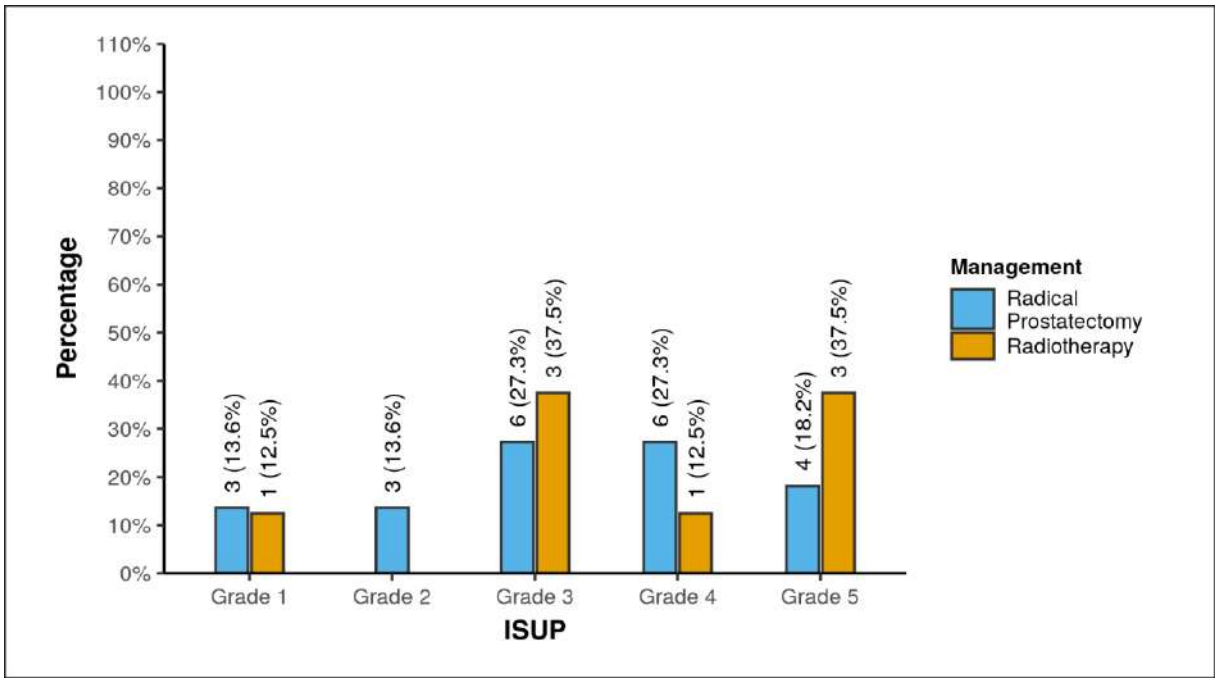


Figure 19a and 19b: Association between RLT and ISUP

Association Between RLT and Clinical T Stage

T Stage (Clinical)	Management			Fisher's Exact Test	
	RP	RT	Total	$\chi 2$	P Value
T2	8 (36.4%)	0 (0.0%)	8 (26.7%)	12.645	0.002
T3a	8 (36.4%)	0 (0.0%)	8 (26.7%)		
T3b	5 (22.7%)	6 (75.0%)	11 (36.7%)		
T4	1 (4.5%)	2 (25.0%)	3 (10.0%)		
Total	22 (100.0%)	8 (100.0%)	30 (100.0%)		

T Stage (Clinical)	Adjusted P Values
T2 vs. T3a	1.000
T2 vs. T3b	0.054
T2 vs. T4	0.082
T3a vs. T3b	0.054
T3a vs. T4	0.082
T3b vs. T4	1.000

Fisher's exact test was used to explore the association between RLT' and Clinical T Stage as more than 20% of the total number of cells had an expected count of less than 5.

There was a **significant difference** between the various groups in terms of distribution of clinical T Stage ($\chi 2 = 12.645$, $p = 0.002$).

Strength of association between the two variables (Cramer's V) = 0.65 (High Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.57 (High Association)

36.4% of the participants in the group [RLT: Radical Prostatectomy] had [T Stage (Clinical): T2]. 36.4% of the participants in the group [RLT: Radical Prostatectomy] had

[T Stage (Clinical): T3a]. 22.7% of the participants in the group [RLT: Radical Prostatectomy] had [T Stage (Clinical): T3b]. 4.5% of the participants in the group [RLT: Radical Prostatectomy] had [T Stage (Clinical): T4]. 0.0% of the participants in the group [RLT: Radiotherapy] had [T Stage (Clinical): T2]. 0.0% of the participants in the group [RLT: Radiotherapy] had [T Stage (Clinical): T3a]. 75.0% of the participants in the group [RLT: Radiotherapy] had [T Stage (Clinical): T3b]. 25.0% of the participants in the group [RLT: Radiotherapy] had [T Stage (Clinical): T4].

Participants in the group RLT: Radical Prostatectomy had the larger proportion of T Stage (Clinical): T2. Participants in the group RLT: Radical Prostatectomy had the larger proportion of T Stage (Clinical): T3a. Participants in the group RLT: Radiotherapy had the larger proportion of T Stage (Clinical): T3b. Participants in the group RLT: Radiotherapy had the larger proportion of T Stage (Clinical): T4.

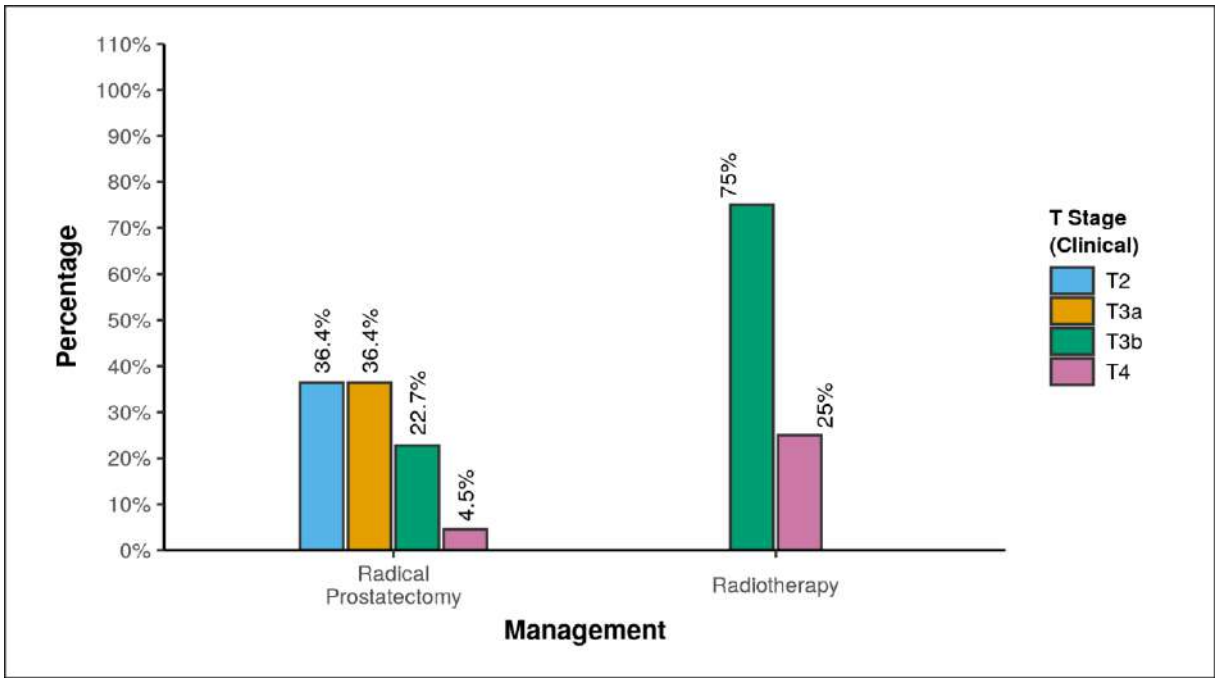
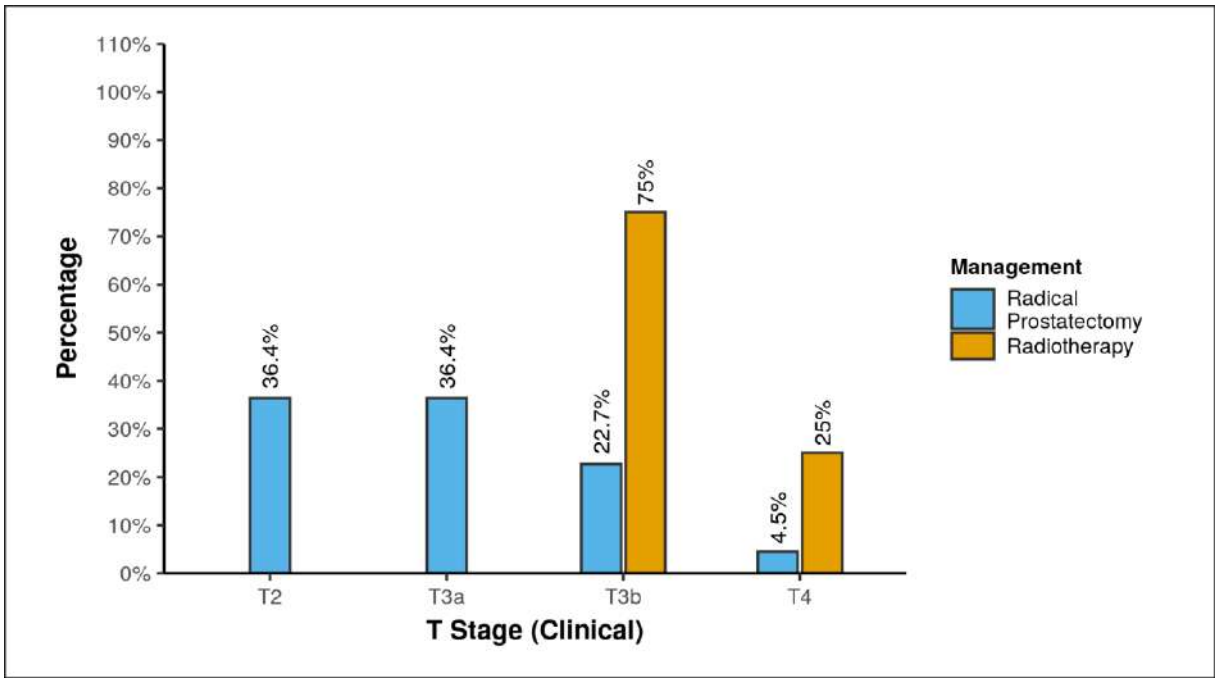


Figure 20a: Association between RLT and Clinical T Stage



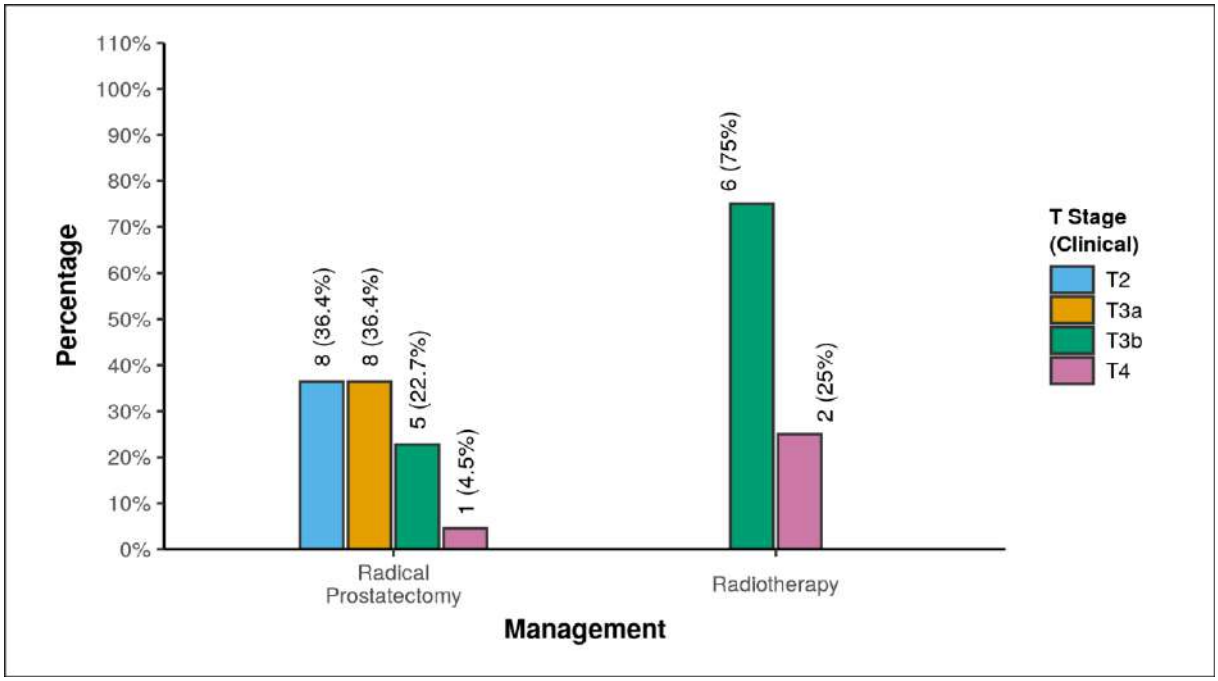


Figure 20b and 20c: Association between RLT and Clinical T Stage

Association Between type of RLT and Preoperative N Stage (Clinical)

N Stage (Clinical)	Management			Fisher's Exact Test	
	RP	RT	Total	χ2	P Value
N0	18 (81.8%)	3 (37.5%)	21 (70.0%)	5.487	0.032
N1	4 (18.2%)	5 (62.5%)	9 (30.0%)		
Total	22 (100.0%)	8 (100.0%)	30 (100.0%)		

Fisher's exact test was used to explore the association between type of RLT and Preoperative N Stage (Clinical) as more than 20% of the total number of cells had an expected count of less than 5.

There was a **significant difference** between the various groups in terms of distribution of preoperative N Stage (Clinical) ($\chi2 = 5.487$, $p = 0.032$).

Strength of association between the two variables (Cramer's V) = 0.43 (Moderate Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.39 (Moderate Association)

81.8% of the participants in the group [RLT: Radical Prostatectomy] had [N Stage (Clinical): N0].

18.2% of the participants in the group [RLT: Radical Prostatectomy] had [N Stage (Clinical): N1].

37.5% of the participants in the group [RLT: Radiotherapy] had [N Stage (Clinical): N0].

62.5% of the participants in the group [RLT: Radiotherapy] had [N Stage (Clinical): N1].

Participants in the group RLT: Radical Prostatectomy had the larger proportion of N Stage N0.

Participants in the group RLT: Radiotherapy had the larger proportion of N Stage (Clinical): N1.

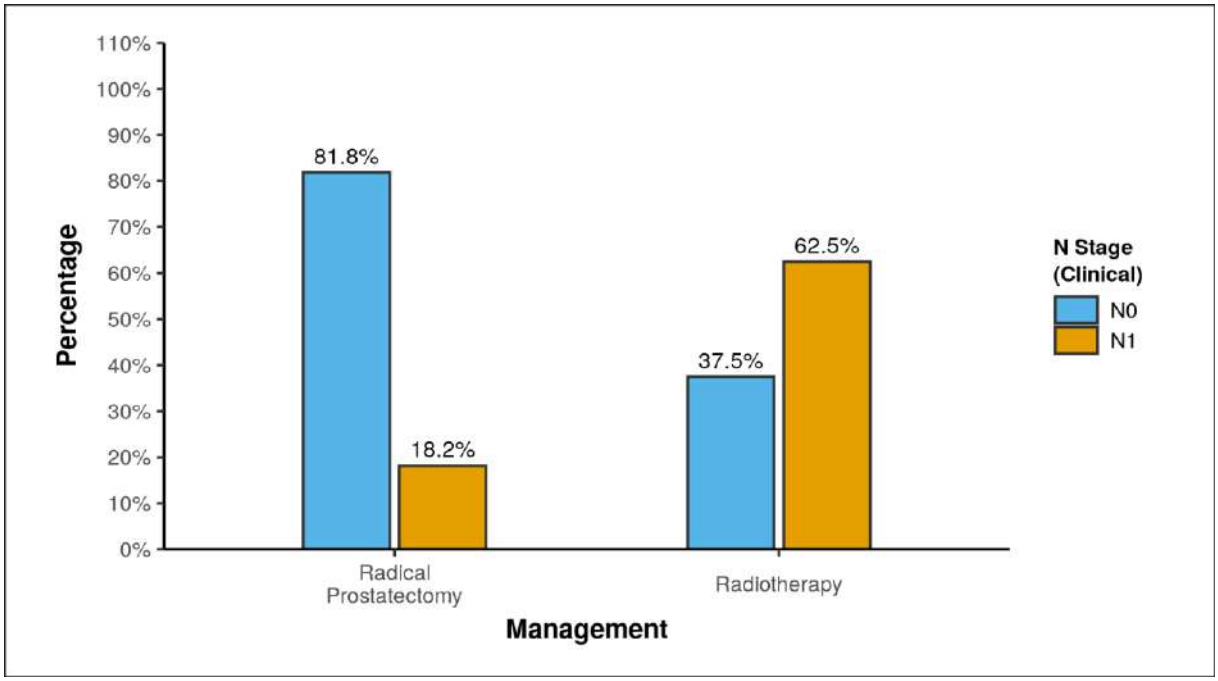


Figure 21a: Association between RLT and Preoperative N Stage (Clinical)

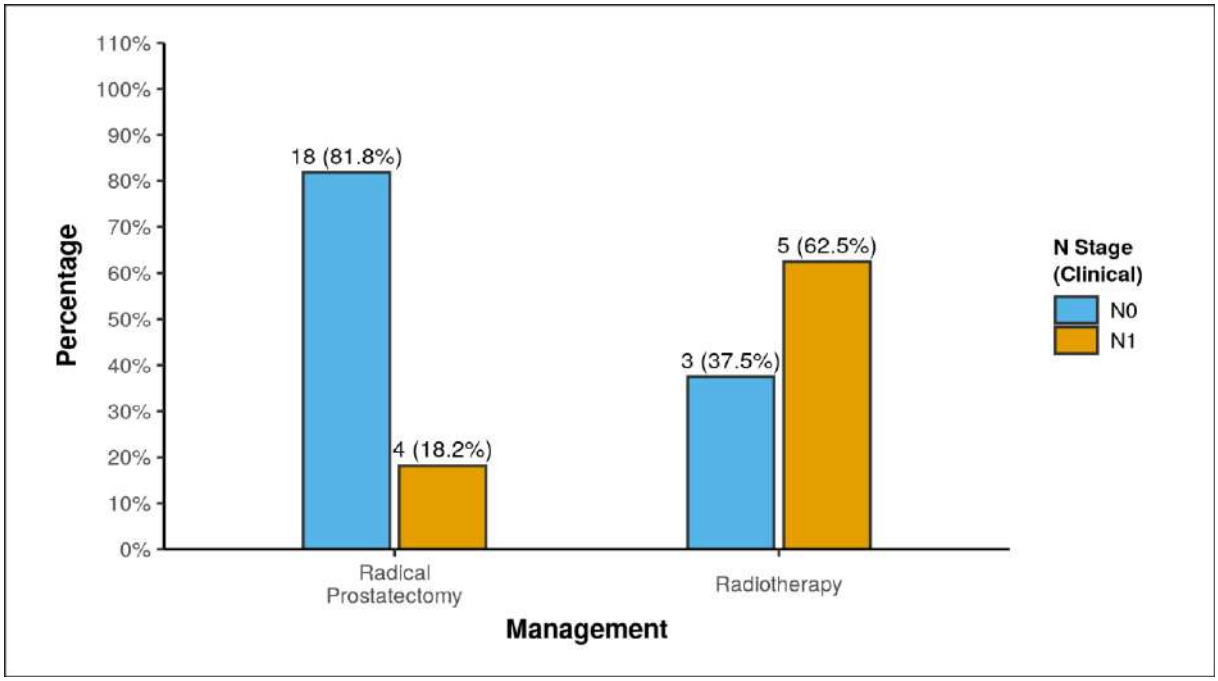


Figure 21b: Association between RLT and preoperative N Stage (Clinical)

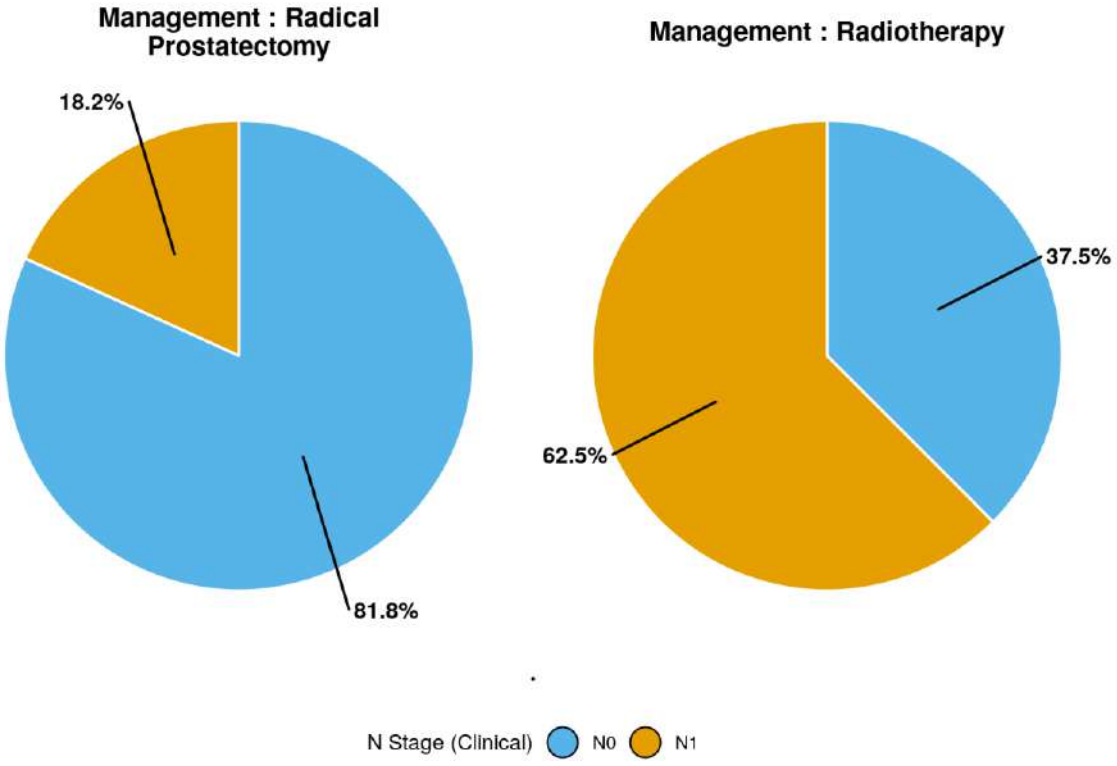


Figure 21b and 21c: Association between RLT and preoperative N Stage (Clinical)

Table 8: **Relative Risks**

Predictor/Risk Factor	Outcome	Relative Risk (95% CI)
N Stage (Clinical): N0	Management: Radical Prostatectomy	1.93 (1.09-4.6)
N Stage (Clinical): N0	Management: Radiotherapy	0.26 (0.08-0.81)
N Stage (Clinical): N1	Management: Radical Prostatectomy	0.52 (0.22-0.92)
N Stage (Clinical): N1	Management: Radiotherapy	3.89 (1.23-12.36)
Management: Radical Prostatectomy	N Stage (Clinical): N0	2.18 (1.1-6.06)
Management: Radical Prostatectomy	N Stage (Clinical): N1	0.29 (0.11-0.82)
Management: Radiotherapy	N Stage (Clinical): N0	0.46 (0.16-0.91)
Management: Radiotherapy	N Stage (Clinical): N1	3.44 (1.22-9.43)

Association Between RLT and M Stage

M Stage	Management			Fisher's Exact Test	
	RP	RT	Total	χ2	P Value
M0	15 (68.2%)	5 (62.5%)	20 (66.7%)	0.085	1.000
M1b	7 (31.8%)	3 (37.5%)	10 (33.3%)		
Total	22 (100.0%)	8 (100.0%)	30 (100.0%)		

Fisher's exact test was used to explore the association between RLT and M Stage as more than 20% of the total number of cells had an expected count of less than 5.

There was no significant difference between the various groups in terms of distribution of M Stage ($\chi 2 = 0.085$, $p = 1.000$).

Strength of association between the two variables (Cramer's V) = 0.05 (No Association)
68.2% of the participants in the group [RLT: Radical Prostatectomy] had [M Stage: M0]. 31.8% of the participants in the group [RLT: Radical Prostatectomy] had [M Stage: M1b]. 62.5% of the participants in the group [RLT: Radiotherapy] had [M Stage: M0]. 37.5% of the participants in the group [RLT: Radiotherapy] had [M Stage: M1b].

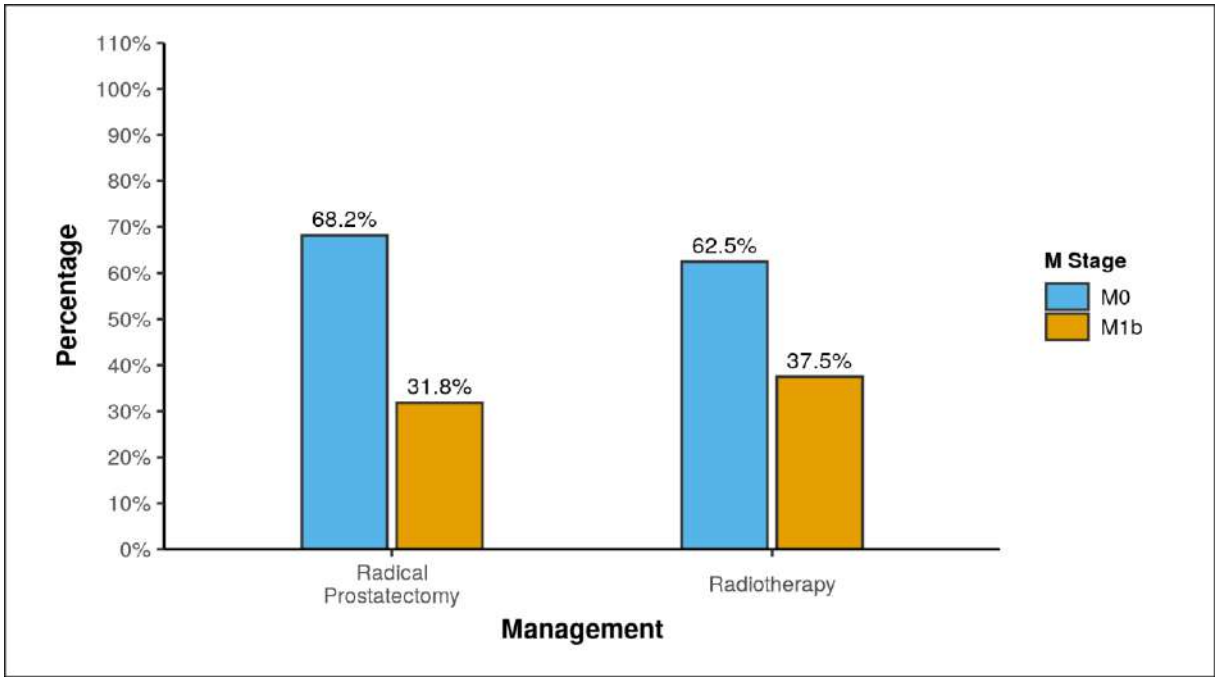


Figure 22: Association between RLT and M Stage

Association between Clinical T Stage and Change in PSA (ng/mL) at 3 Months

Change in PSA (ng/mL) (3 Months)	T Stage (Clinical)					Kruskal Wallis Test	
	T2	T3a	T3b	T4		$\chi 2$	p value
Mean (SD)	-19.70 (8.98)	-46.72 (43.22)	-53.31 (53.37)	-99.63 (NA)		9.620	0.047
Median (IQR)	-17.46 (-26.99--13.99)	-34.3 (-51.34--24.44)	-29.86 (-55.98--23.03)	-99.63 (-99.63--99.63)			
Min - Max	-33.96 - -6.8	-141.93 - -5.88	-202.98 - -17.75	-99.63 - -99.63			

The variable Change in PSA (ng/mL) at 3 Months) was not normally distributed in the 5 subgroups of the variable Clinical T Stage. Thus, non-parametric tests (Kruskal Wallis Test) were used to make group comparisons.

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T2 group was -19.70 (8.98).

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T3a group was -46.72 (43.22).

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T3b group was -53.31 (53.37). The mean (SD) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage : T4 group was -99.63 (NA).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T2 group was -17.46 (-26.99--13.99).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T3a group was -34.3 (-51.34--24.44).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T3b group was -29.86 (-55.98--23.03).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the Clinical T Stage: T4 group was -99.63 (-99.63--99.63).

There was a **significant difference** between the 4 groups in terms of **Change in PSA** (ng/mL) at 3 Months ($\chi 2 = 9.620$, $p = 0.047$), with the median Change in PSA (ng/mL) at 3 Months being highest in the Clinical T Stage: T2 group. Strength of Association (Kendall's Tau) = 0.41 (Medium Effect Size)

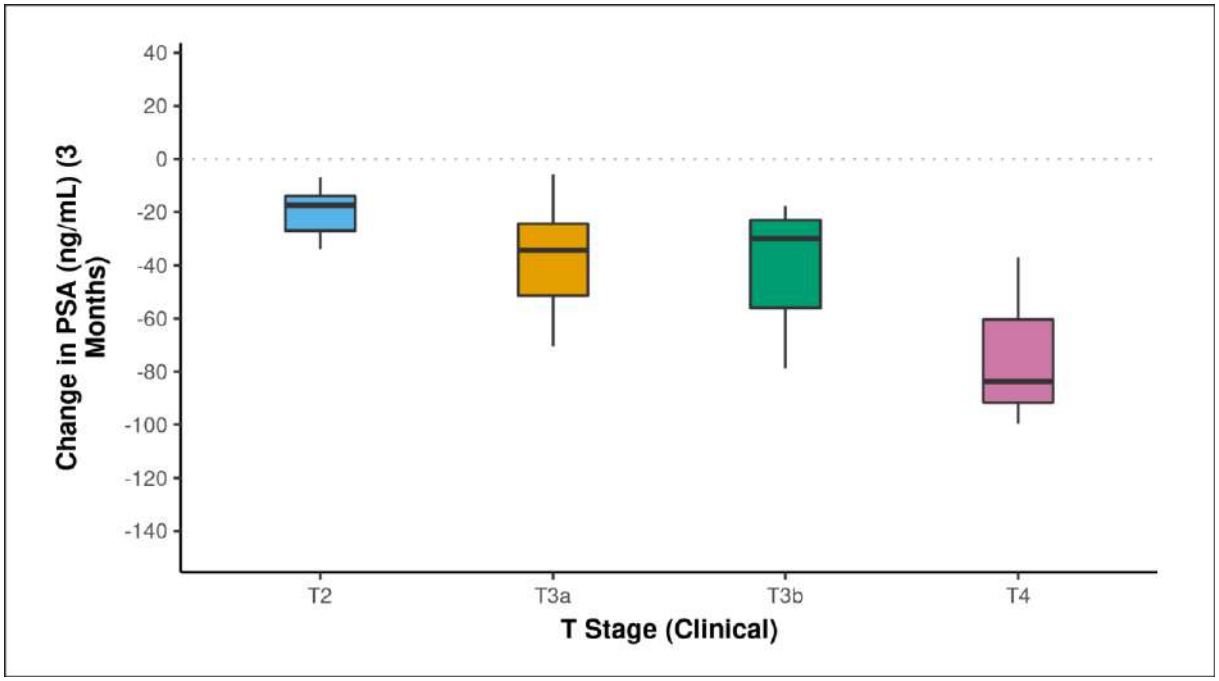


Figure 23: Association Between Clinical T Stage and Change in PSA (ng/mL) at 3 Months

Association between Preoperative N Stage and Change in PSA (ng/mL) at 3 Months

Change in PSA (ng/mL) (3 Months)	N Stage (Clinical)		Wilcoxon-Mann-Whitney U Test	
	N0	N1	W	p value
Mean (SD)	-33.33 (29.65)	-70.92 (57.11)	145.000	0.022
Median (IQR)	-27 (-38.85--14.96)	-60.97 (-83.77--28.98)		
Min - Max	-141.93 - -5.88	-202.98 - -22.21		

The variable Change in PSA (ng/mL) at 3 Months was not normally distributed in the 2 subgroups of the variable preoperative N Stage (Clinical). Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of Change in PSA (ng/mL) (3 Months) in the N Stage (Clinical): N0 group was -33.33 (29.65).

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the preoperative N Stage (Clinical): N1 group was -70.92 (57.11).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the preoperative N Stage (Clinical): N0 group was -27 (-38.85--14.96).

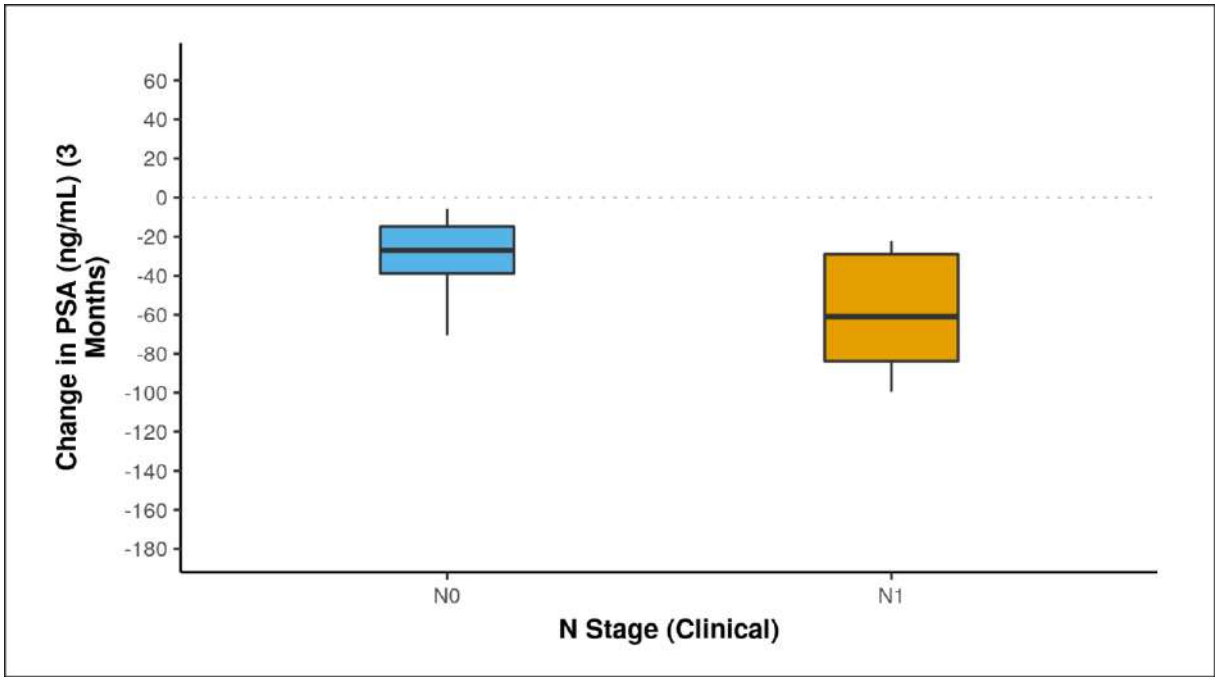
The median (IQR) of Change in PSA (ng/mL) at 3 Months in the preoperative N Stage (Clinical): N1 group was -60.97 (-83.77--28.98).

There was a **significant difference** between the 2 groups in terms of **Change in PSA** (ng/mL) **at 3 Months** (W = 145.000, p = 0.022), with the median Change in PSA (ng/mL) at 3 Months being highest in the preoperative N Stage (Clinical): N0 group.

Strength of Association (Point-Biserial Correlation) = 0.41 (Large Effect Size)

The Box-and-Whisker plot below depicts the distribution of Change in PSA (ng/mL) at 3 Months in the 2 groups. The middle horizontal line represents the median Change in PSA

(ng/mL)at 3 Months, the upper and lower bounds of the box represent the 75th and the 25th centile of Change in PSA (ng/mL)at 3 Months respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Change in PSA (ng/mL) at 3 Months in each of the groups.



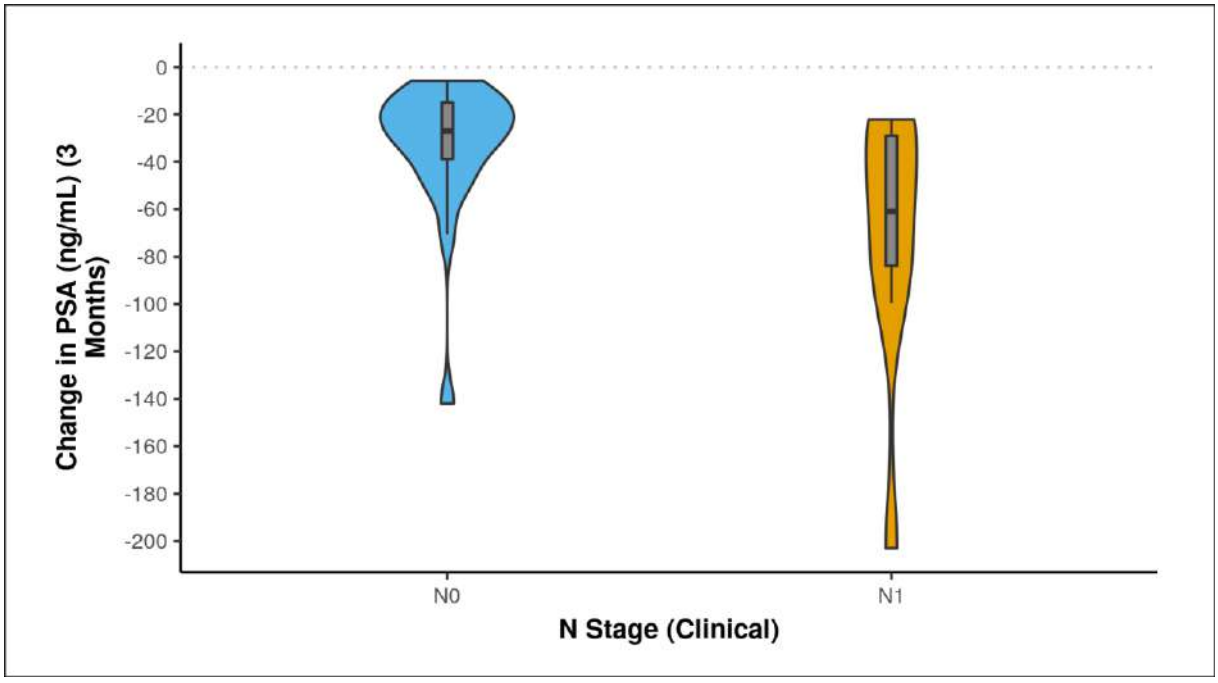


Figure 24a and 24b: Association Between Preoperative N Stage (Clinical) and Change in PSA (ng/mL) at 3 Months

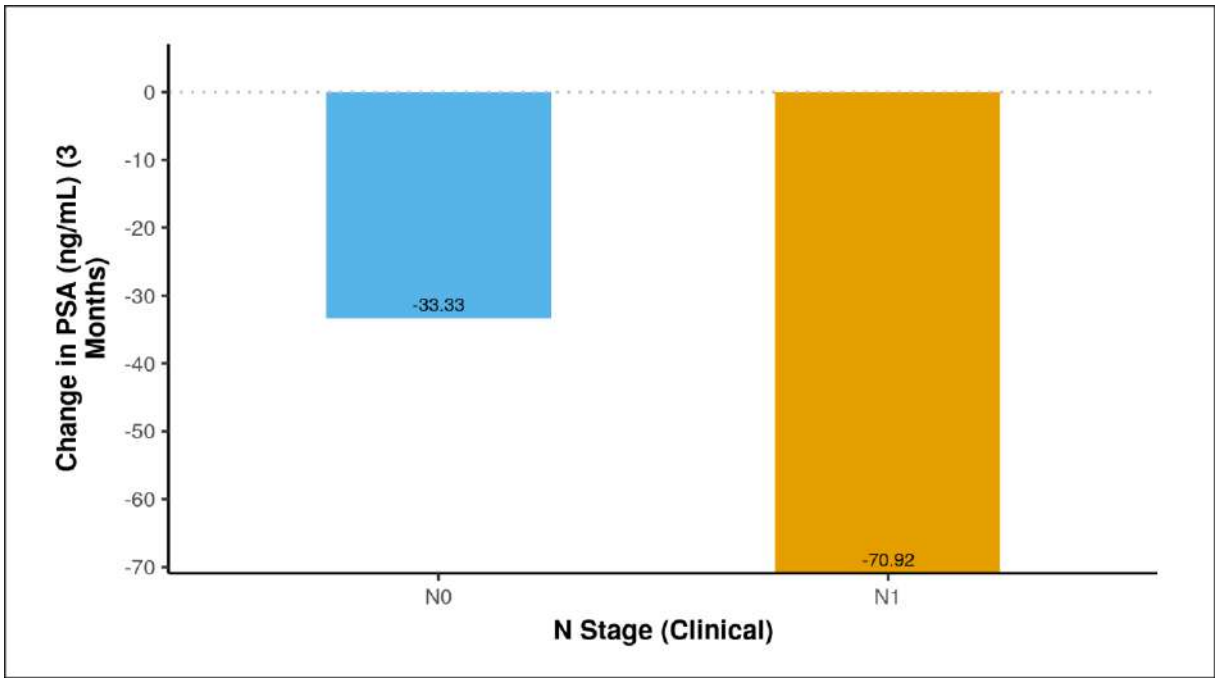


Figure 24c: Association Between Preoperative N Stage (Clinical) and Change in PSA (ng/mL) at 3 Months

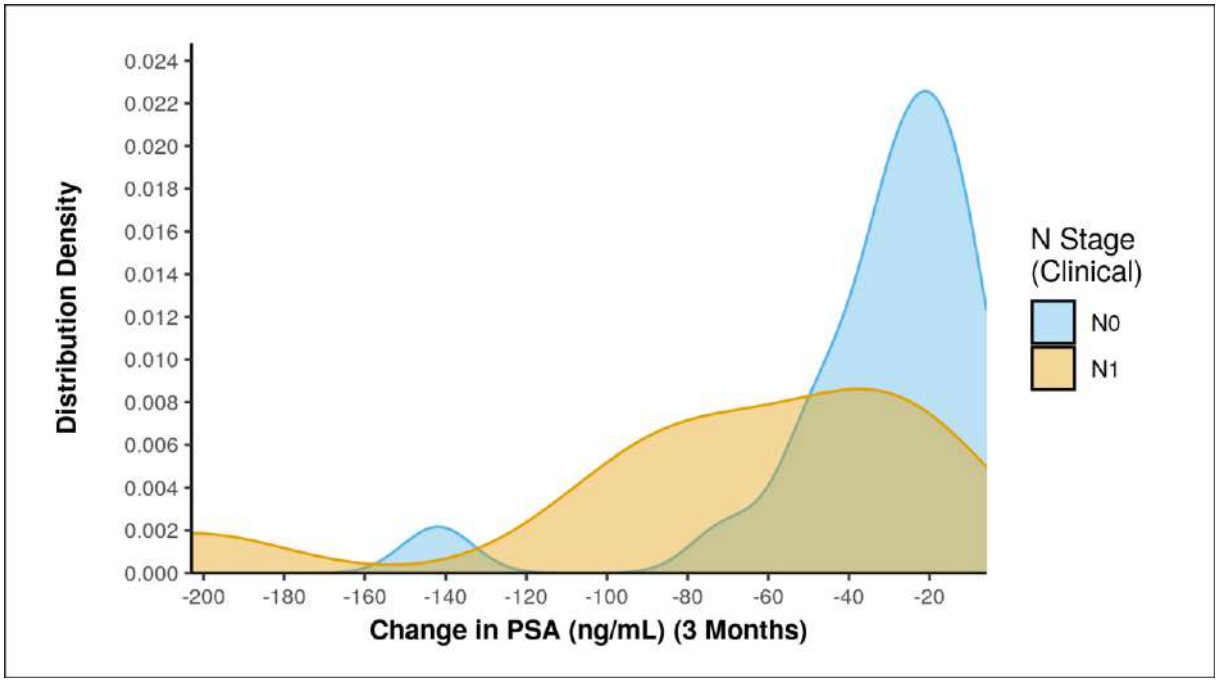


Figure 24d: Association Between N Stage (Clinical) and Change in PSA (ng/mL) (3 Months)

Association between M Stage and Change in PSA (ng/mL) at 3 Months

Change in PSA (ng/mL) (3 Months)	M Stage		Wilcoxon-Mann-Whitney U Test	
	M0	M1b	W	p value
Mean (SD)	-53.30 (47.15)	-27.21 (25.38)	46.000	0.017
Median (IQR)	-35.48 (-55.87--26.9)	-16.36 (-26.99--13.99)		
Min - Max	-202.98 - -13.97	-83.77 - -5.88		

The variable Change in PSA (ng/mL) at 3 Months was not normally distributed in the 2 subgroups of the variable M Stage. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the M Stage: M0 group was -53.30 (47.15).

The mean (SD) of Change in PSA (ng/mL) at 3 Months in the M Stage: M1b group was -27.21 (25.38).

The median (IQR) of Change in PSA (ng/mL) at 3 Months in the M Stage: M0 group was -35.48 (-55.87--26.9).

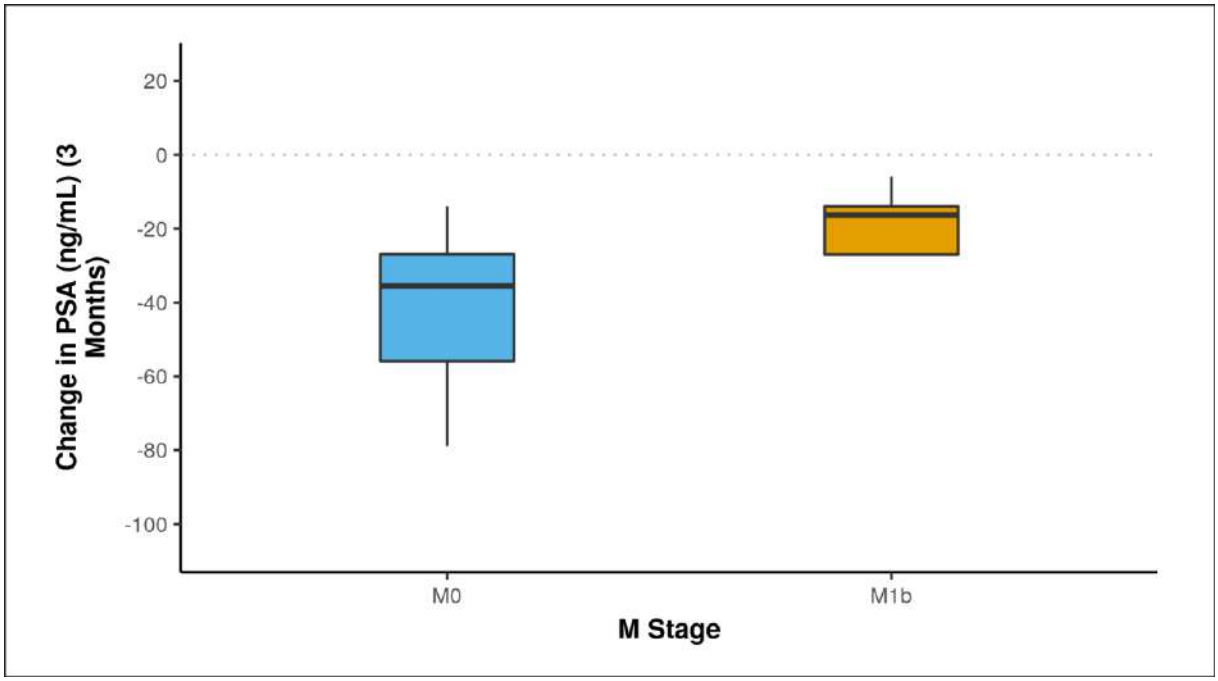
The median (IQR) of Change in PSA (ng/mL) at 3 Months in the M Stage: M1b group was -16.36 (-26.99--13.99).

There was a **significant difference** between the 2 groups in terms of Change in PSA (ng/mL) at 3 Months (W = 46.000, p = 0.017), with the median Change in PSA (ng/mL) (3 Months) being highest in the M Stage: M1b group.

Strength of Association (Point-Biserial Correlation) = 0.29 (Medium Effect Size)

The Box-and-Whisker plot below depicts the distribution of Change in PSA (ng/mL) at 3 Months in the 2 groups. The middle horizontal line represents the median Change in PSA

(ng/mL) at 3 Months , the upper and lower bounds of the box represent the 75th and the 25th centile of Change in PSA (ng/mL) at 3 Months respectively, and the upper and lower extent of the whiskers represent the Tukey limits for Change in PSA (ng/mL) at 3 Months in each of the groups.



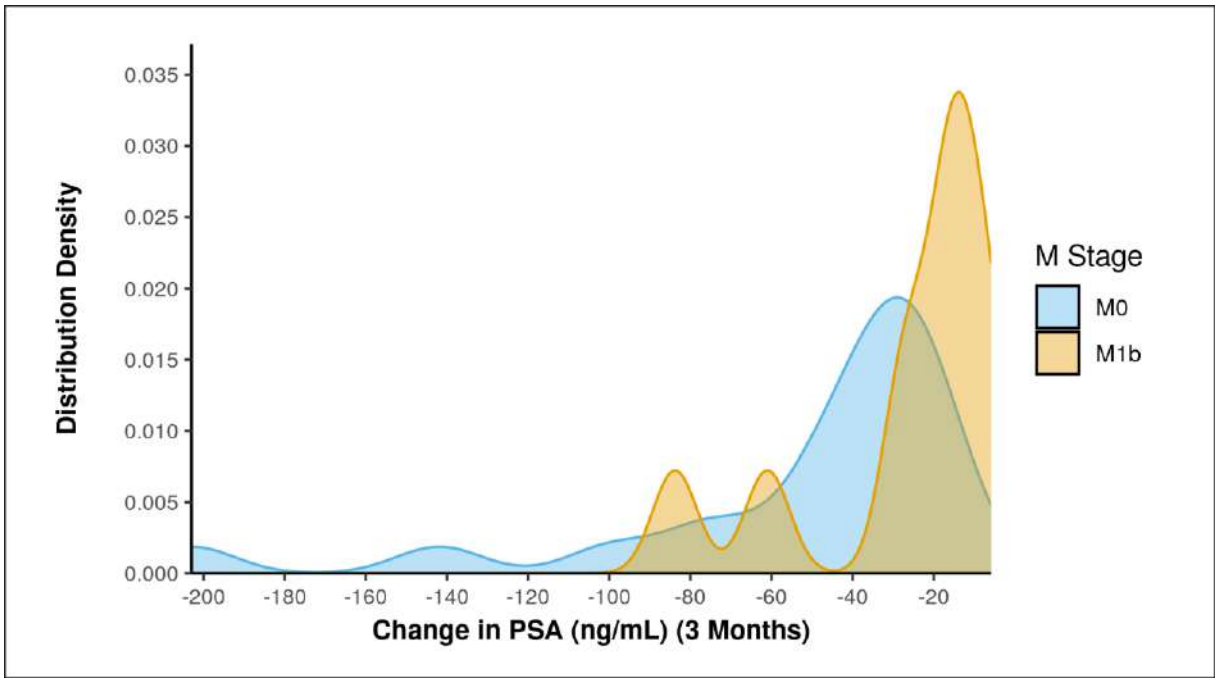


Figure 25a and 25b: Association Between M Stage and Change in PSA (ng/mL) at 3 Months

Association between Number of Metastases and Change in PSA (ng/mL) at 3 Months

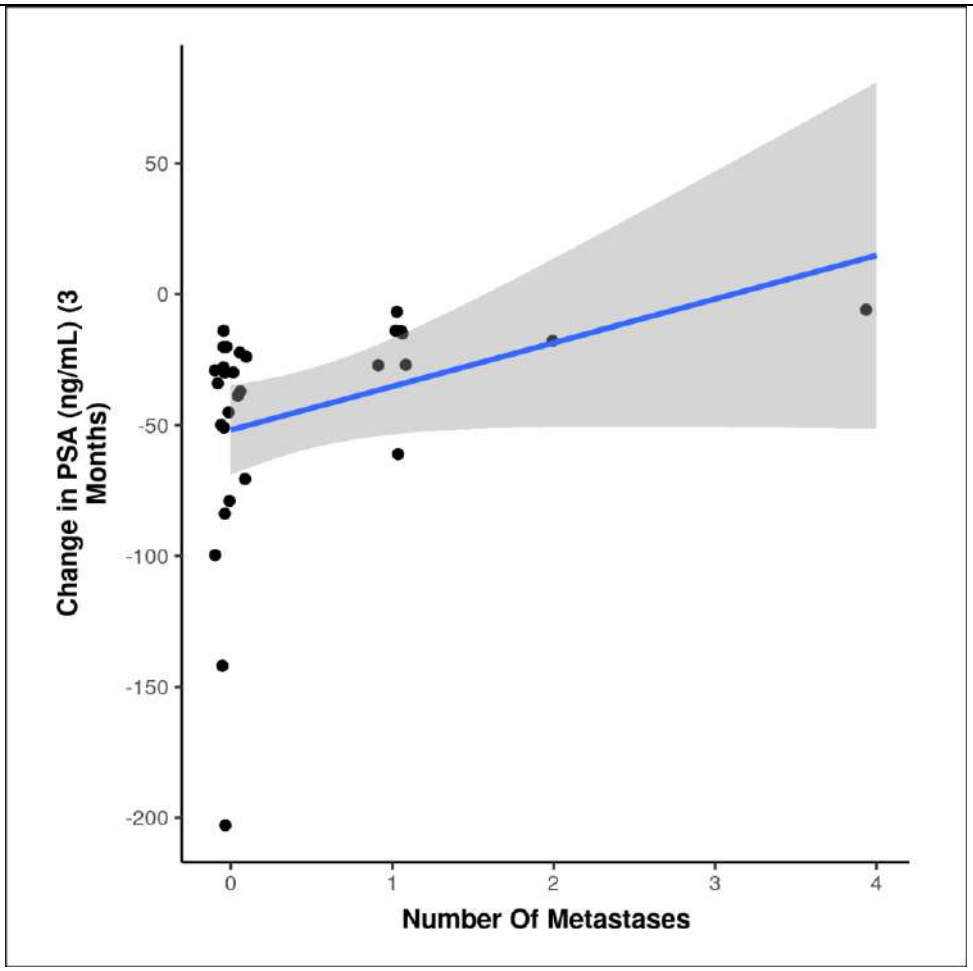


Figure 26: Association between Number of Metastases and Change in PSA (ng/mL) at 3 Months

Correlation	Spearman Correlation Coefficient	P Value
Number Of Metastases vs Change in PSA (ng/mL) (3 Months)	0.57 (95%CI: 0.22 to 0.79)	0.001

The above scatterplot depicts the correlation between Number of Metastases and Change in PSA (ng/mL) at 3 Months.

Individual points represent individual cases. The blue trend-line represents the general trend of correlation between the two variables. The shaded grey area represents the 95% confidence interval of this trend-line.

Non-parametric tests (Spearman Correlation) were used to explore the correlation between the two variables, as at least one of the variables was not normally distributed.

There was a **moderate positive correlation** between Number of Metastases and Change in PSA (ng/mL) at 3 Months, and this correlation was statistically significant (rho = 0.57, p = 0.001).

For every 1 unit increase in Number of Metastases, the Change in PSA (ng/mL) at 3 Months increases by 16.67 units.

Change in PSA (ng/mL) (3 Months) = 51.83 + 16.67*Number of Metastases

Conversely, for every 1 unit increase in Change in PSA (ng/mL) at 3 Months, the Number of Metastases increases by 0.01 units.

Number Of Metastases = 0.74 + 0.01*Change in PSA (ng/mL) at 3 Months

Comparison of the two Groups in Terms of change in PSA (ng/mL) over Time

PSA (ng/mL)	Management		P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Radical Prostatectomy	Radiotherapy	
	Mean (SD)	Mean (SD)	
Initial	39.68 (32.96)	59.62 (62.24)	0.412
3 Months	0.50 (1.18)	0.10 (0.10)	0.639
P Value for change in PSA (ng/mL) over time within each group (Wilcoxon Test)	<0.001	0.008	

PSA (ng/mL)	Management		P value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	Radical Prostatectomy	Radiotherapy	
	Mean (SD)	Mean (SD)	
Overall P Value for comparison of change in PSA (ng/mL) over time between the two groups (Generalized Estimating Equations)	0.349		

Non-Parametric tests were used to make statistical inference as data were not normally distributed. Wilcoxon-Mann-Whitney Test test was used to compare the two groups at each of the timepoints (right-most column in the table above). Wilcoxon signed-rank test was used to explore the difference in PSA (ng/mL) between the time points within each group (second-last row in the table above). Generalized Estimating Equations method was used to explore the difference in change in PSA (ng/mL) between the two groups over time (last row in the table above).

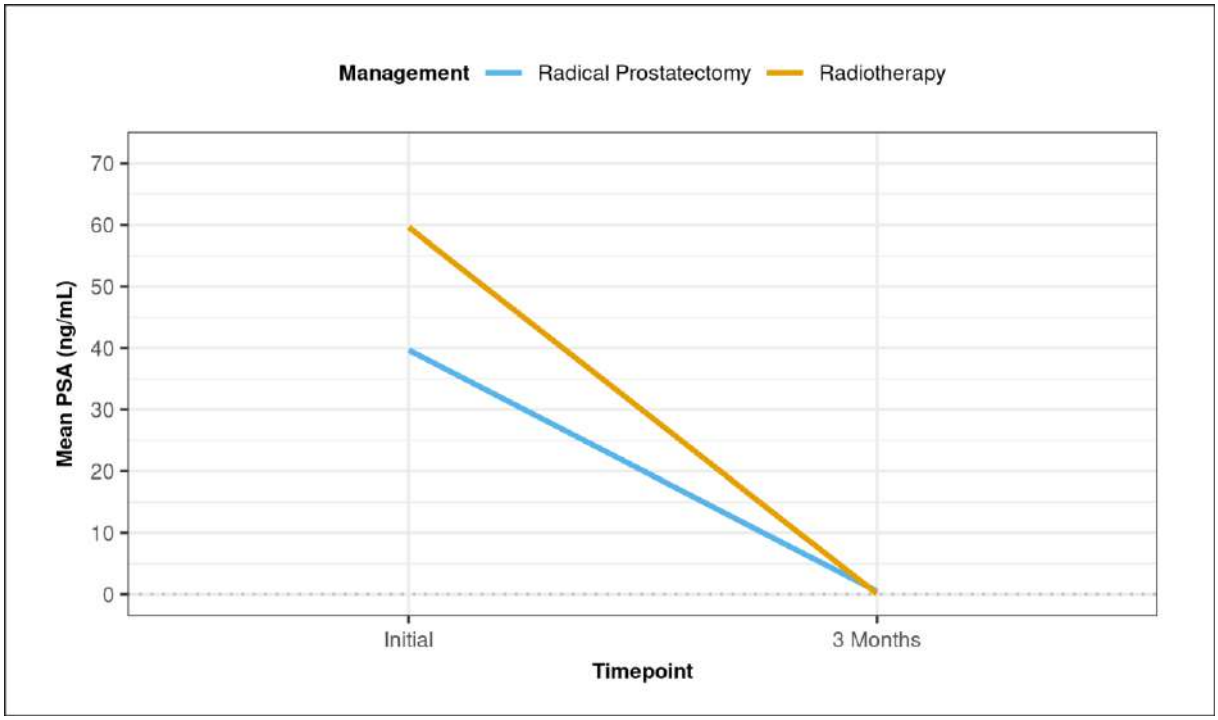
The two groups did not differ in terms of PSA (ng/mL) at any of the timepoints.

In the Radical Prostatectomy group, the mean PSA (ng/mL) decreased from a maximum of 39.68 at the Initial time point to a minimum of 0.50 at the 3 Months time point. This change was statistically significant (Wilcoxon Test: V = 253.0, p = <0.001).

In the Radiotherapy group, the mean PSA (ng/mL) decreased from a maximum of 59.62 at the Initial time point to a minimum of 0.10 at the 3 Months time point. This change was statistically significant (Wilcoxon Test: V = 36.0, p = 0.008).

The overall change in PSA (ng/mL) over time was compared in the two groups using the Generalized Estimating Equations method. There was no significant difference in the trend of PSA (ng/mL) over time between the two groups (p = 0.349).

The following is a line diagram depicting the change in PSA (ng/mL) over time in the two groups.



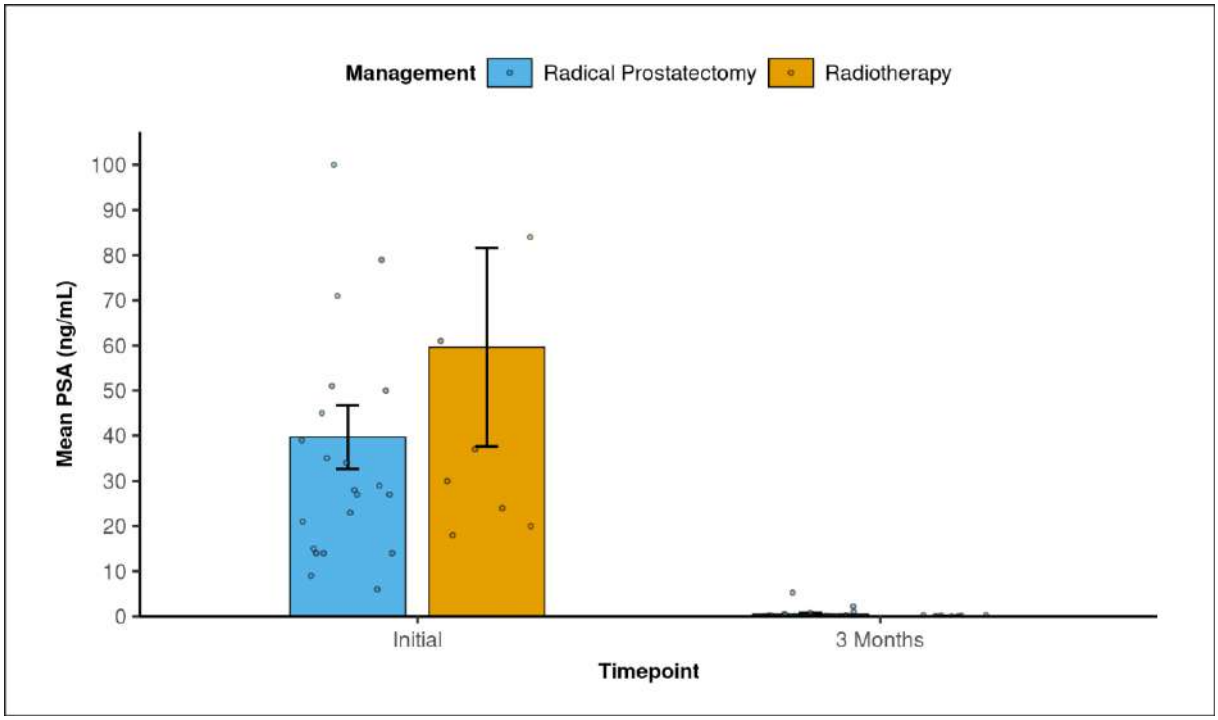


Figure 27a and 27b: Change in PSA (ng/mL) Over Time

Association Between ADT and Clinical T Stage

T Stage (Clinical)	ADT			Fisher's Exact Test	
	Yes	No	Total	$\chi 2$	P Value
T2	0 (0.0%)	8 (42.1%)	8 (36.4%)	11.811	0.013
T3a	0 (0.0%)	8 (42.1%)	8 (36.4%)		
T3b	2 (66.7%)	3 (15.8%)	5 (22.7%)		
T4	1 (33.3%)	0 (0.0%)	1 (4.5%)		
Total	3 (100.0%)	19 (100.0%)	22 (100.0%)		

T Stage (Clinical)	Adjusted P Values
T2 vs. T3a	1.000
T2 vs. T3b	0.192
T2 vs. T4	0.192
T3a vs. T3b	0.192
T3a vs. T4	0.192
T3b vs. T4	1.000

Fisher's exact test was used to explore the association between ADT and Clinical T Stage as more than 20% of the total number of cells had an expected count of less than 5.

There was a **significant difference** between the various groups in terms of distribution of T Stage (Clinical) ($\chi 2 = 11.811$, $p = 0.013$).

Strength of association between the two variables (Cramer's V) = 0.73 (High Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.64 (High Association)

0.0% of the participants in the group [ADT: Yes] had [T Stage (Clinical): T2]. 0.0% of the participants in the group [ADT: Yes] had [T Stage (Clinical): T3a]. 66.7% of the participants in the group [ADT: Yes] had [T Stage (Clinical): T3b]. 33.3% of the participants in the group [ADT: Yes] had [T Stage (Clinical): T4]. 42.1% of the

participants in the group [ADT: No] had [T Stage (Clinical): T2]. 42.1% of the participants in the group [ADT: No] had [T Stage (Clinical): T3a]. 15.8% of the participants in the group [ADT: No] had [T Stage (Clinical): T3b]. 0.0% of the participants in the group [ADT: No] had [T Stage (Clinical): T4].

Participants who received ADT in the adjuvant setting predominantly had Clinical stage T3b and T4.

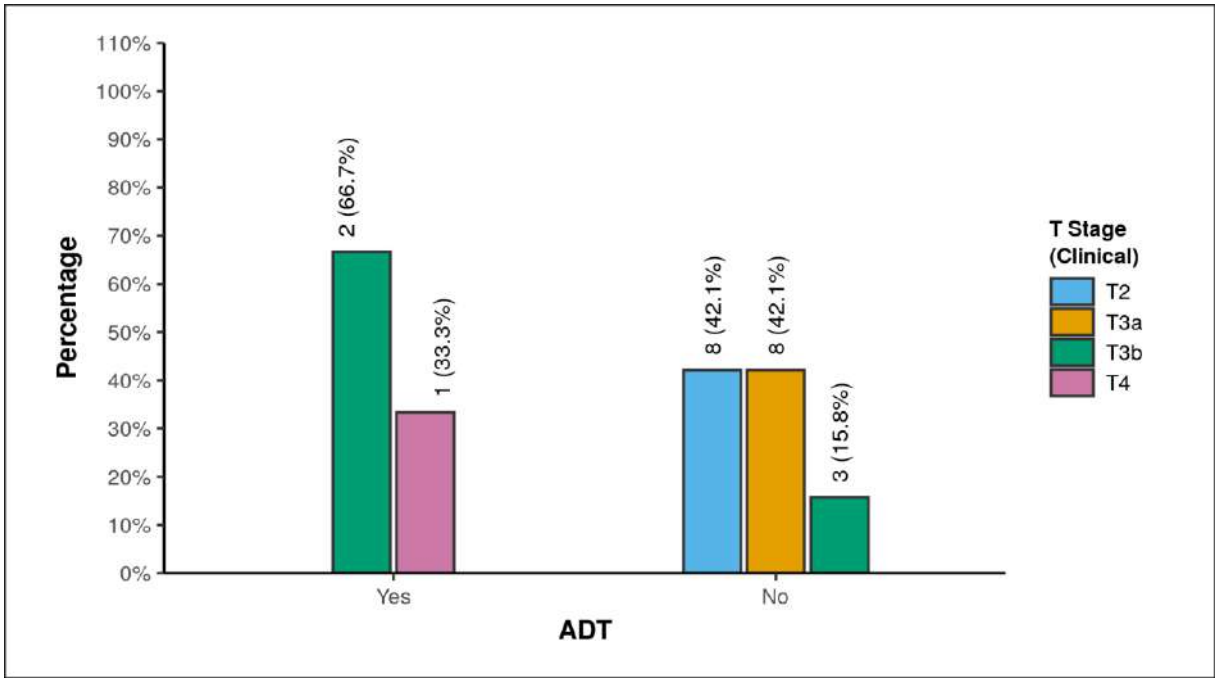


Figure 28: Association between ADT and Clinical T Stage

Association Between ADT and Preoperative N Stage (Clinical)

N Stage (Clinical)	ADT			Fisher's Exact Test	
	Yes	No	Total	$\chi 2$	P Value
N0	0 (0.0%)	18 (94.7%)	18 (81.8%)	15.632	0.003
N1	3 (100.0%)	1 (5.3%)	4 (18.2%)		
Total	3 (100.0%)	19 (100.0%)	22 (100.0%)		

Fisher's exact test was used to explore the association between 'ADT' and 'N Stage (Clinical)' as more than 20% of the total number of cells had an expected count of less than 5.

There was a **significant difference** between the various groups in terms of distribution of N Stage (Clinical) ($\chi 2 = 15.632$, $p = 0.003$).

Strength of association between the two variables (Cramer's V) = 0.84 (High Association)

Strength of association between the two variables (Bias Corrected Cramer's V) = 0.83 (High Association)

0.0% of the participants in the group [ADT: Yes] had [N Stage (Clinical): N0]. 100.0% of the participants in the group [ADT: Yes] had [N Stage (Clinical): N1]. 94.7% of the participants in the group [ADT: No] had [N Stage (Clinical): N0]. 5.3% of the participants in the group [ADT: No] had [N Stage (Clinical): N1].

Participants in the group ADT: No had the larger proportion of N Stage (Clinical): N0.

Participants in the group ADT: Yes had the larger proportion of N Stage (Clinical): N1.

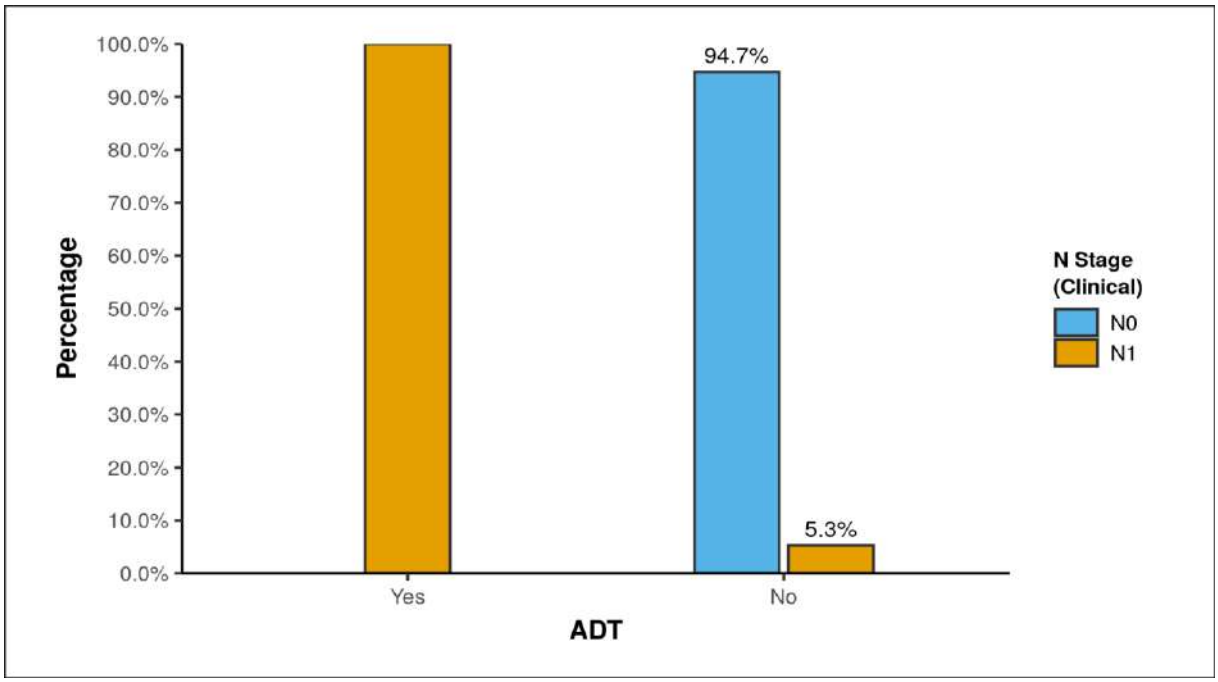


Figure 29: Association between ADT and Preoperative N Stage (Clinical)

Relative Risks

Predictor/Risk Factor	Outcome	Relative Risk (95% CI)
N Stage (Clinical): N0	ADT: Yes	0 (0-0.25)
N Stage (Clinical): N0	ADT: No	4 (1.43-21.94)
N Stage (Clinical): N1	ADT: Yes	Inf (3.95-Inf)
N Stage (Clinical): N1	ADT: No	0.25 (0.05-0.7)
ADT: Yes	N Stage (Clinical): N0	0 (0-0.6)
ADT: Yes	N Stage (Clinical): N1	19 (3.5-106.93)
ADT: No	N Stage (Clinical): N0	Inf (1.67-Inf)
ADT: No	N Stage (Clinical): N1	0.05 (0.01-0.29)

Association between Margins and PSA (ng/mL) at 3 Months

PSA (ng/mL) (3 Months)	Margins		Wilcoxon-Mann-Whitney U Test	
	Positive	Negative	W	p value
Mean (SD)	1.71 (2.40)	0.23 (0.53)	60.000	0.045
Median (IQR)	0.77 (0.39-2.09)	0.06 (0.01-0.14)		
Min - Max	0.05 - 5.26	0 - 2.2		

The variable PSA (ng/mL) at 3 Months was not normally distributed in the 2 subgroups of the variable Margins. Thus, non-parametric tests (Wilcoxon-Mann-Whitney U Test) were used to make group comparisons.

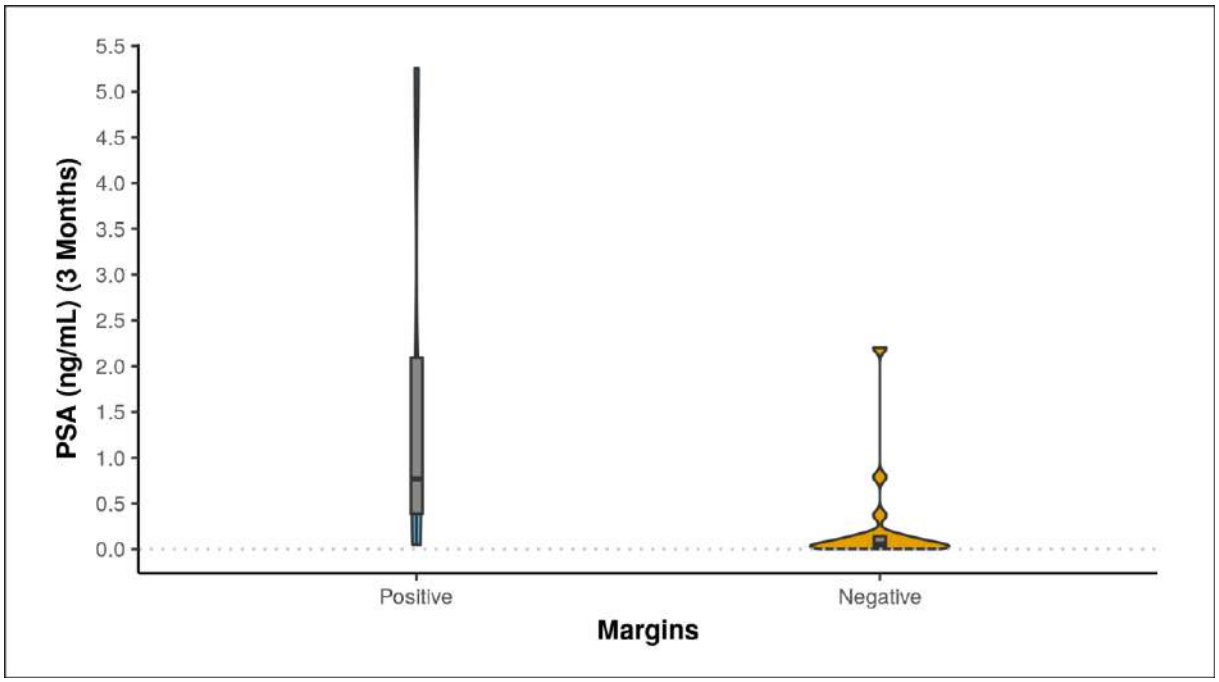
The mean (SD) of PSA (ng/mL) at 3 Months in the Margins: Positive group was 1.71 (2.40). The mean (SD) of PSA (ng/mL) at 3 Months in the Margins: Negative group was 0.23 (0.53). The median (IQR) of PSA (ng/mL) at 3 Months in the Margins: Positive group was 0.77 (0.39-2.09). The median (IQR) of PSA (ng/mL) at 3 Months in the Margins: Negative group was 0.06 (0.01-0.14). The PSA (ng/mL) at 3 Months in the Margins: Positive ranged from 0.05 - 5.26. The PSA (ng/mL) at 3 Months in the Margins: Negative ranged from 0 - 2.2.

There was a **significant difference** between the 2 groups in terms of PSA (ng/mL) at 3 Months (W = 60.000, p = 0.045), with the median PSA (ng/mL) (3 Months) being highest in the Margins: Positive group.

Strength of Association (Point-Biserial Correlation) = 0.5 (Large Effect Size)

The Box-and-Whisker plot below depicts the distribution of PSA (ng/mL) at 3 Months in the 2 groups. The middle horizontal line represents the median PSA (ng/mL) at 3 Months, the upper and lower bounds of the box represent the 75th and the 25th centile of PSA

(ng/mL) at 3 Months respectively, and the upper and lower extent of the whiskers represent the Tukey limits for PSA (ng/mL) at 3 Months in each of the groups.



The bar graph below depicts the means of PSA (ng/mL) (3 Months) in the 2 different groups.

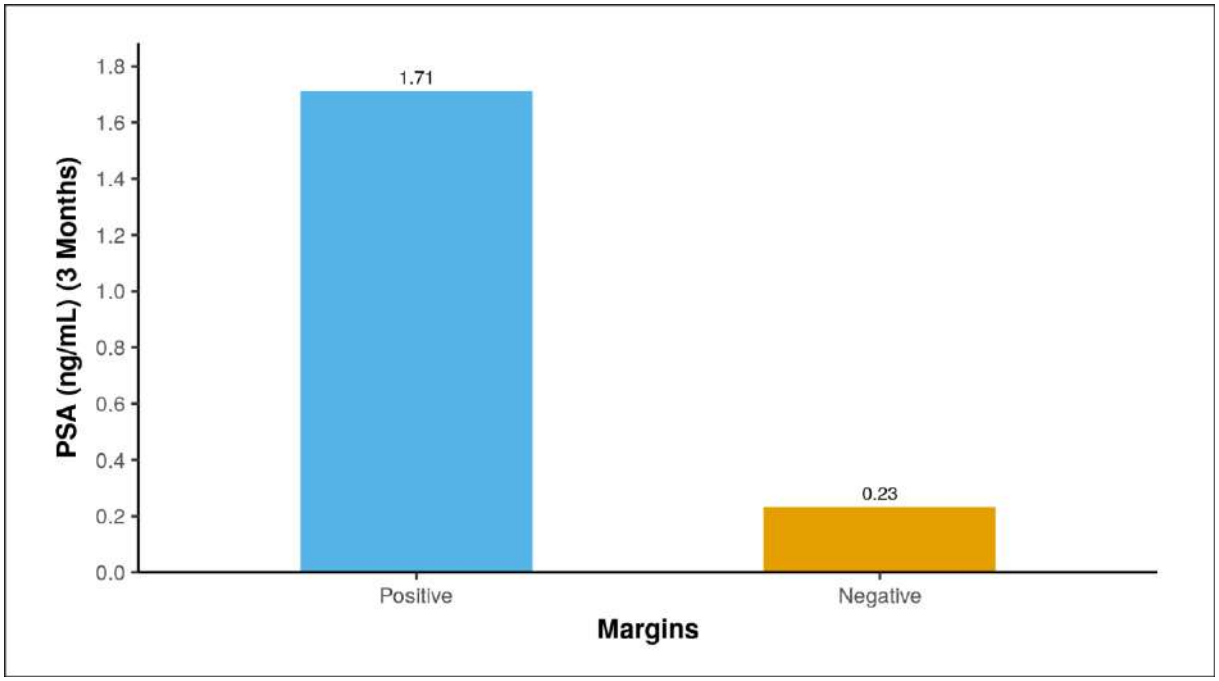


Figure 30a and 30b: Association Between Margins and PSA (ng/mL) at 3 Months

Summary Table for Association between RLT and Parameters

Parameters	Management		p value
	Radical Prostatectomy (n = 22)	Radiotherapy (n = 8)	
Age (Years)	62.73 ± 7.92	67.62 ± 7.07	0.095[1]
Age			0.391[2]
40-49 Years	2 (9.1%)	0 (0.0%)	
50-59 Years	4 (18.2%)	1 (12.5%)	
60-69 Years	12 (54.5%)	3 (37.5%)	
70-79 Years	4 (18.2%)	4 (50.0%)	
PSA (ng/mL) (Initial)	39.68 ± 32.96	59.62 ± 62.24	0.412[1]
PSA (ng/mL) (3 Months)	0.50 ± 1.18	0.10 ± 0.10	0.639[1]
Change in PSA (ng/mL) (3 Months)	-39.18 ± 33.10	-59.52 ± 62.27	0.368[1]
Percent Change in PSA (ng/mL) (3 Months)	-97.59 ± 5.92	-99.64 ± 0.47	0.368[1]
PIRADS score			0.335[2]
PIRADS 3	2 (10.0%)	0 (0.0%)	
PIRADS 4	4 (20.0%)	0 (0.0%)	
PIRADS 5	14 (70.0%)	8 (100.0%)	
ISUP			0.751[2]
Grade 1	3 (13.6%)	1 (12.5%)	
Grade 2	3 (13.6%)	0 (0.0%)	
Grade 3	6 (27.3%)	3 (37.5%)	
Grade 4	6 (27.3%)	1 (12.5%)	
Grade 5	4 (18.2%)	3 (37.5%)	
T Stage (Clinical)* **			<0.001[2]
T2	8 (36.4%)	0 (0.0%)	
T3a	8 (36.4%)	0 (0.0%)	
T3b	5 (22.7%)	6 (75.0%)	
T4	1 (4.5%)	2 (25.0%)	
T Stage (Pathological)* **			0.019[2]
T2	8 (36.4%)	0 (0.0%)	
T3a	3 (13.6%)	0 (0.0%)	
T3b	11 (50.0%)	6 (75.0%)	

Parameters	Management		p value
	Radical Prostatectomy (n = 22)	Radiotherapy (n = 8)	
T4	0 (0.0%)	2 (25.0%)	
N Stage (Clinical)* **			0.032 [2]
N0	18 (81.8%)	3 (37.5%)	
N1	4 (18.2%)	5 (62.5%)	
N Stage (Pathological)			0.210 [2]
N0	15 (68.2%)	3 (37.5%)	
N1	7 (31.8%)	5 (62.5%)	
M Stage			1.000 [2]
M0	15 (68.2%)	5 (62.5%)	
M1b	7 (31.8%)	3 (37.5%)	
Number Of Metastases	0.45 ± 0.91	0.38 ± 0.74	0.838 [1]
Clavien Dindo Classification			1.000 [3]
Grade 1	14 (63.6%)	0 (NaN%)	
Grade 2	5 (22.7%)	0 (NaN%)	
Grade 3	3 (13.6%)	0 (NaN%)	
LVI (Yes)	2 (9.1%)	1 (12.5%)	1.000 [2]
PNI (Yes)	17 (77.3%)	7 (87.5%)	1.000 [2]
Margins (Positive)	4 (18.2%)	0 (NaN%)	1.000 [3]
ADT (Yes)	3 (13.6%)	0 (NaN%)	1.000 [3]
Comments			1.000 [3]
Bladder Neck Sparing	2 (66.7%)	0 (NaN%)	
Lost To Follow Up	1 (33.3%)	0 (NaN%)	

****Significant at p<0.05, 1: Wilcoxon-Mann-Whitney U Test, 2: Fisher's Exact Test*

The following variables were significantly associated (p<0.05) with the variable type of management, radical local therapy that was given (RP or EBRT): T Stage (Clinical), N Stage (Clinical).

DISCUSSION

1.Descriptive Parameters

Management Approaches in LAPC and OMPCa

In our study 73.3% of patients underwent radical prostatectomy, with 26.7% receiving radiotherapy. Similar management strategies were observed in a study by Fossati et al.[147], where radical prostatectomy was preferred for locally advanced prostate cancer, showing significant long-term benefits in terms of metastasis-free survival. This proclivity also aligns with findings from Heidenreich and Pfister, who advocate radical cytoreductive prostatectomy in scenarios typified by oligometastatic disease, bolstering long-term oncological outcomes[148]. The g-RAMPP study further elucidates this theme, as it juxtaposes radical prostatectomy combined with the best systemic therapy against solely systemic approaches, emphasising comprehensive disease management for patients harbouring up to five bone metastases[142]. Radiotherapy's role, particularly in oligometastatic settings, was highlighted in a multicenter study by Löppenberg et al., which demonstrated its efficacy in local control and symptom palliation[149].

This distribution reflects the increasing use of RLT, in LAPC and OMPCa, aligning with the trend seen in studies like TROMBONE and Gandaglia et al., where local treatments were explored in this specific cohort of patients[7,150].

Age Distribution

The median age of 65 years in our study is reflective of the typical at-risk demographic. This is consistent with findings by Cooperberg et al.[151], where the median age of diagnosis was around 64 years, emphasising that age, expected life span and performance status remains a are key factor in prostate cancer prognosis and treatment d[151]. Similar age range

was also reported in the FUSCC OMPca study, both studies reflect the typical demographic most at risk for prostate cancer[142,151].

PSA Levels

The initial mean PSA level in our study was 45.00 ng/mL, reinforcing the aggressive nature of the disease within our cohort, an observation that finds consonance in the work of Wallis et al.[152.] Initial mean PSA levels in our study were higher than those reported in the GRAMMP study, which recorded a lower median initial PSA level[142]. This disparity may reflect variations in disease severity, racial or ethnic predilections, or subjectivity of diagnostic practices between the cohorts. The initial PSA levels in our study varied widely, ranging from 6 to 203 ng/mL. This is similar to that observed in the HORRAD and STAMPEDE trials[8,12], where patients presented with a broad spectrum of PSA levels, reflecting different stages of disease burden.

Three-month post-treatment PSA levels in our study showed effective reduction, a finding echoed by the Trombone trial, which demonstrated the efficacy of RP in ameliorating PSA levels in patients with OMPCa[7].

PIRADS and ISUP Grading

The prevalence of high PIRADS and ISUP grades in our cohort is comparable to that in a study by Hamdy et al.[153], which linked higher grades with increased aggressiveness and poorer clinical outcomes, advocating for the use of these grading systems to guide treatment intensity and modalities.

The majority of our patients were classified under PIRADS 5(78.6 %) and had higher ISUP grades, suggesting advanced and aggressive disease. This is in consonace to the data from the study by Gandaglia et al., which reported a predominance of high-grade disease in

patients with OMPCa undergoing radical prostatectomy. This comparison underscores the critical nature of PIRADS and ISUP grading in guiding treatment decisions.

In our study, 4 patients were categorised as ISUP Grade 1, with 3 undergoing radical prostatectomy and 1 receiving radiotherapy. Similarly, 7 patients were classified as ISUP Grade 5, of which 4 underwent radical prostatectomy, while 3 were treated with radiotherapy. Among the ISUP Grade 1 patients who had radical prostatectomy, two presented with single osseous metastases (M1b). Clinical staging, based on digital rectal examination (DRE) and imaging, indicated that the disease was localized. Following thorough discussions of treatment options and prioritising patient preferences, the decision to proceed with radical prostatectomy was made.

Additionally, 4 of the 7 patients with ISUP Grade 5 also underwent radical prostatectomy. Among these, 3 did not exhibit osseous metastases, although imaging revealed locally advanced yet resectable disease. One patient, however, had a solitary osseous metastasis in the right pubic bone. In these cases, the decision to proceed with surgery was made after shared decision-making and careful consideration of all options.

This scenario underscores the inherent limitations and potential discrepancies between imaging and biopsy results, which may stem from subjective interpretation, variations in biopsy techniques, or other influencing factors. Notably, a disease that appears localised on imaging may still harbour occult metastases, undetectable at the time of diagnosis. Conversely, a cancer that is deemed locally advanced may not necessarily be associated with distant metastases. These nuances highlight the complexity of disease staging and the importance of not relying solely on imaging or biopsy results in isolation. Consequently, a more sophisticated, individualised approach is required—one that integrates comprehensive patient discussions, multidisciplinary assessments, and a robust shared

decision-making process to ensure optimal treatment strategies are tailored to each patient's unique circumstances.

T, N, and M Staging

In terms of clinical staging, 36.7% of participants had T3b disease, and 10.0% had T4, with a similar distribution in pathological staging. This is consistent with findings from Karim et al.[154], where a significant proportion of oligometastatic patients had locally advanced disease (T3-T4). Moreover, 30.0% of participants in our study had nodal involvement (N1), comparable to the high nodal involvement reported by Gratzke et al.[10], who emphasised the prognostic significance of lymph node status in advanced prostate cancer.

Our study also revealed a disparity between clinical and pathological T staging in the Radical Prostatectomy subgroup, wherein T stage was upstaged from a clinical T2/T3a based on examination and imaging to pT3b in the pathological specimen in 6 patients. This finding is similar to Sooriakumaran et al.'s retrospective analysis, which demonstrated that advanced T-stage at diagnosis was associated with worse outcomes despite aggressive treatment[7,15]. This further highlights the critical role of imaging in these patients.
. Comparative N and M staging data from our study also reflect findings by James et al., where advanced N and M stages were associated with lower survival rates, stressing the importance of early detection and comprehensive staging[155].

Lastly, 33.3% of our participants had bone metastases (M1b), which parallels the oligometastatic focus of the TROMBONE and Gandaglia et al. studies, where patients typically had limited bone metastases[7,150]. In our study, the mean number of metastases was 0.47, with a range of 0 to 4, consistent with the definition of oligometastatic disease used in the literature. This is also similar to patient cohort in the HORRAD trial. HORRAD also included patients with more extensive metastatic disease, but they found that the number of metastases played a role in determining benefits of local therapy[12].

2. All Results, Outcomes, and Associations:

PSA Decline

Post-treatment PSA reduction in our study is in concordance with the findings by Tendulkar et al., showing effective disease control with RLT[156].In our study, the mean PSA at 3 months post-treatment was 0.40 ng/mL, showing a significant decline, which reflects effective local control. This finding are in agreement with TROMBONE, where PSA levels decreased significantly following radical prostatectomy in oligometastatic patients, and with STAMPEDE, where local radiotherapy resulted in better PSA control in patients with a low metastatic burden[7,8]. Similarly, HORRAD reported improved PSA progression-free survival, though not overall survival, in patients treated with radiotherapy[12]. Likewise, in the Gandaglia et al. cohort, RP resulted in long-term biochemical control, despite a high rate of margin positivity[150].

Surgical Margins:

In our study, positive surgical margins were associated with poorer PSA outcomes at 3 months, reflecting the need for R0 resection improve outcomes. This finding conforms with the study by Gandaglia et al., where 73% of patients had positive surgical margins, a common challenge in OMPCa. Despite this, long-term cancer-specific survival was reported as high as 82 %. Gratzke et al. also stressed the critical role of negative margins, as patients with positive margins faced higher rates of recurrence and progression[10].

Survival and Progression-Free Outcomes:

While overall survival (OS) and progression-free survival (PFS) were not the primary endpoints in our study, the strong association between PSA decline and surgical margins suggests that these factors could influence long-term outcomes. In STAMPEDE, local treatment with radiotherapy improved failure-free survival in patients with low metastatic

burden, a group similar to our cohort[8]. HORRAD did not find an OS benefit with radiotherapy in patients with extensive metastases, but the improved BCR suggested that local treatment has a role in OMPCa[12]. Gandaglia et al. reported a 7-year cancer-specific mortality-free survival rate of 82%, reinforcing the value of local treatment in selected oligometastatic patients[150].

Comparison of Local Therapy Approaches:

In TROMBONE, radical prostatectomy was found to be a feasible and safe approach for OMPCa, with significant PSA declines and good oncologic outcomes, mirroring the findings in our study[7]. STAMPEDE primarily focused on RT and its impact on patients with low metastatic burden, showing that local treatment can be beneficial in controlling disease progression. Gandaglia et al. and Karim et al. both supported the role of RP in managing OMPCa, coupled with SOC, reinforcing the findings from our study that highlight the importance of combining radical prostatectomy or radiotherapy with systemic therapies[150,154].The management of LAPC and OMPCa represents a dynamic frontier in oncology, where the integration of RLT with systemic treatments offers new dimension for improved patient outcomes. The shifting paradigm, driven by a deeper understanding of the disease's biology and the advent of advanced diagnostic tools, has allowed for more precise targeting of therapies that extend beyond traditional systemic approaches.

This thesis underscores the importance of a multimodal approach, advocating for the aggressive management of the primary tumor in selected patients to potentially reduce the overall tumor burden and impede the metastatic cascade. The concept of oligometastatic disease, characterized by a limited number of metastatic sites, has emerged as a distinct clinical entity with specific therapeutic needs and prognostic outcomes.

LIMITATIONS AND FUTURE PROSPECTS

During the course of this thesis on the management of locally advanced and OMPCa, several significant limitations were identified that impacted the research conclusions and their broader applicability:

1. Limited Sample Size: The primary limitation encountered was the small sample size, which constrains the generalisability of the findings.

2. Variation in Surgical Techniques: The thesis did not adequately distinguish between different surgical methods—laparoscopic, open, and robotic radical prostatectomies. As the medical field increasingly adopts robotic-assisted surgeries for their precision and reduced recovery times, it is imperative for subsequent research to explicitly compare these techniques to determine their specific impacts on patient outcomes.

3.Confounders in Radiotherapy Evaluation: The evaluation of EBRT's efficacy within this thesis was complicated by the concurrent use of ADT, making it difficult to isolate the benefits of radiotherapy alone.

4.Lack of Advanced Imaging Techniques: This study did not employ advanced imaging techniques like PSMA PET scans, potentially leading to less precise disease staging and assessment. Incorporating advanced imaging modalities in future research is essential for accurate disease evaluation and tailored treatment planning.

5.Inadequate Long-term Follow-up: The limited follow-up period of three months in this study is insufficient to fully evaluate long-term treatment outcomes. For RLT such as radiotherapy, the most significant declines in PSA typically become apparent after a period of at least twelve months. Although the initial decline in serum PSA can serve as a useful surrogate marker to gauge the response to treatment in this cohort of patients, it does not

provide insight into long-term outcomes. This brief follow-up period was a necessary limitation of this student thesis project, as longer follow-up was not feasible within the academic timeframe. Future research efforts should aim for extended follow-up durations to more accurately assess the enduring impacts of treatment protocols and to better understand the progression and management of the disease over time.

CONCLUSION

The integration of RLT such as radical prostatectomy and radiation therapy with systemic treatments offers significant promise for managing LAPC and OMPCa.These therapies have demonstrated efficacy, safety, and no significant short-term adverse effects, establishing them as feasible treatment modalities for this patient cohort.

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Appendix -1

Study Proforma

Title of the study- A prospective observational study to evaluate biochemical response of radical local

therapies in patients with locally advanced or oligometastatic carcinoma prostate

Patient's serial no.:

CR No.:

Age:

Sex:

Occupation:

Chief Complaints:

Duration of complaints:

Comorbid Illness:

Personal history:

Laboratory parameters:

CBC-

RFT-

LFT-

Blood Sugar-

Coagulation Profile-

Viral Serology-

Serum PSA

Urine routine-

Urine culture-

Radiological investigation:

Chest Xray

Ultrasonography of Kidney, Ureter, Bladder with post void residual (USG KUB with post void residual) findings:

Kidney-

Ureter-

Bladder-

Prostate- size, echogenicity

Post void residual urine-

Any other findings-

mpMRI Prostate findings:

PIRADS score:

Bone Scan or PSMA PET Findings

HPE findings (TRUS BIOPSY)

ECG and 2D Echo

PAC Fitness for Radical Prostatectomy Or EBRT

Appendix -2

Patient Information Sheet

1.STUDY TITLE: A Prospective Observational Study to Evaluate Biochemical Response of Radical Local Therapies (Radical Prostatectomy or EBRT) in Patients with Locally Advanced or Oligometastatic Carcinoma Prostate.

2. STUDY INVESTIGATORS:

Student: Dr. Udit Khurana, Senior resident (Mch), Department of Urology.

Guide: Dr Kumar Madhavan

Co-Guide/s: Dr Devashish Kaushal, Dr. Saikat Das

3. Introduction:

We are conducting a research study to evaluate biochemical response of radical local therapies (Radical Prostatectomy Or EBRT) in patients with locally advanced or oligometastatic carcinoma prostate.

This study is being conducted at AIIMS, Bhopal.

4. Purpose of the study:

To assess the efficacy of radical local therapy, i.e, EBRT or Radical Prostatectomy in patients with locally advanced and oligometastatic carcinoma prostate.

What is locally advanced and oligometastatic prostate cancer?

Locally advanced prostate cancer is defined as T3 to T4 disease that has spread to involve one or several of the following: prostate capsule, seminal vesicles, regional pelvic lymph nodes, or adjacent organs such as the bladder, rectum, or pelvic wall.

Oligometastatic prostate cancer (OMPC), generally defined by presence of five or fewer metastatic sites on imaging, represents a transitional state between localised and widespread metastatic disease and encompasses a wide spectrum of disease biologies and clinical behaviours.

5.What is Radical Prostatectomy?

The main type of surgery for prostate cancer is a **radical prostatectomy**. In this operation, the surgeon removes the entire prostate gland plus some of the tissue around it, including the seminal vesicles.

Radical retropubic prostatectomy

For this open operation, the surgeon makes an incision (cut) in your lower abdomen, from the umbilicus down to the pubic bone.

Laparoscopic radical prostatectomy

For a laparoscopic radical prostatectomy (LRP), the surgeon inserts special long instruments through several small incisions in the abdominal wall to remove the prostate. One of the instruments has a small video camera on the end, which lets the surgeon see inside the body. Laparoscopic prostatectomy has some advantages over open radical prostatectomy, including less blood loss and pain, shorter hospital stays (usually no more than a day), faster recovery times, and the catheter will need to remain in the bladder for less time.

Risks and complications associated with Radical Prostatectomy

Risks of prostate surgery

Problems during or shortly after the operation can include:

- Reactions to anaesthesia
- Bleeding from the surgery
- Blood clots in the legs or lungs
- Damage to nearby organs
- Infections at the surgery site.
- Rarely, part of the intestine might be injured during surgery, which could lead to infections in the abdomen and might require more surgery to fix. Injuries to the

intestines are more common with laparoscopic surgeries than with the open approach.

- If lymph nodes are removed, a collection of lymph fluid (called a lymphocele) can form and may need to be drained.

Side effects of prostate surgery

- **Urinary incontinence** (being unable to control urine or leakage or dribbling of urine. Being incontinent can affect you not only physically but emotionally and socially as well.

- **Erectile dysfunction** (impotence; problems getting or keeping erections sufficient for sexual penetration)

Erections are controlled by 2 tiny bundles of nerves that run on either side of the prostate. If you can have erections before surgery, the surgeon will try not to injure these nerves during the prostatectomy. This is known as a **nerve-sparing** approach. But if the cancer is growing into or very close to the nerves, the surgeon will need to remove them.

Your ability to have an erection after surgery depends on your age, your ability to get an erection before the operation, and whether the nerves were cut. All men can expect some decrease in the ability to have an erection, but the younger you are, the more likely it is that you will keep this ability.

If your ability to have erections does return after surgery, it often returns slowly. In fact, it can take from a few months up to 2 years. During the first few months, you will probably not be able to have a spontaneous erection, so you may need to use medicines or other treatments.

There are several options for treating erectile dysfunction:

- **Phosphodiesterase-5 (PDE5) inhibitors** such as sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), and avanafil (Stendra) are pills that can help with

erections. These drugs won't work if both nerves that control erections have been damaged or removed.

- **Alprostadil** is a man-made version of prostaglandin E1, a substance naturally made in the body that can produce erections. It can be injected almost painlessly into the base of the penis 5 to 10 minutes before intercourse or placed into the tip of the penis as a suppository. You can even increase the dosage to prolong the erection.
- **Vacuum devices** are another option to create an erection. These mechanical pumps are placed over the penis. The air is sucked out of the pump, which draws blood into the penis to produce an erection.
- **Penile implants** might restore your ability to have erections if other methods don't help. An operation is needed to put them inside the penis. There are several types of penile implants, including those using silicone rods or inflatable devices.

Changes in orgasm: After surgery, the sensation of orgasm should still be pleasurable, but there is no ejaculation of semen – the orgasm is "dry."

Loss of fertility: Radical prostatectomy cuts the vas deferens, which are the pathways between the testicles (where sperm are made) and the urethra (through which sperm leave the body). Your testicles will still make sperm, but they can't leave the body as a part of the ejaculate. This means that a man can no longer father a child the natural way. Often, this is not an issue, as men with prostate cancer tend to be older. But if it is a concern for you, you might want to ask your doctor about "banking" your sperm before the operation.

Lymphedema: This is a rare but possible complication of removing many of the lymph nodes around the prostate. Lymphedema can usually be treated with physical therapy, although it may not go away completely.

Change in penis length: A possible effect of surgery is a small decrease in penis length. This is probably due to a shortening of the urethra when a portion of it is removed along with the prostate.

Inguinal hernia: A prostatectomy increases a man's chances of developing an inguinal (groin) hernia in the future.

6.What is EBRT?

In EBRT, beams of radiation are focused on the prostate gland from a machine outside the body. You will usually go for treatment 5 days a week in an outpatient centre for at least four weeks. Each treatment is much like getting an x-ray. The radiation is stronger than that used for an x-ray, but the procedure typically is painless. Each treatment lasts only a few minutes, although the setup time — getting you into place for treatment — takes longer. Newer EBRT techniques focus the radiation more precisely on the tumour. This allows higher doses of radiation to be given to the the tumour while reducing the radiation exposure to nearby healthy tissues.

Adverse Effects associated with EBRT:

Bowel problems: Radiation can irritate the rectum and cause a condition called **radiation proctitis**. This can lead to diarrhoea, sometimes with blood in the stool, and rectal leakage. To help lessen bowel problems, you may be told to follow a special diet during radiation therapy to help limit bowel movement during treatment. Sometimes a balloon-like device or gel is put between the rectum and the prostate before treatment to act like a spacer to lessen the amount of radiation that reaches the rectum.

Urinary problems: Radiation can irritate the bladder and lead to a condition called **radiation cystitis**. You might need to urinate more often, have a burning sensation while you urinate, and/or find blood in your urine. Rarely, the tube that carries urine from the bladder out of the body (the urethra) may become very narrow or even close off, which is known as a urethral stricture. This might require further treatment to open it up again.

Feeling tired: Radiation therapy can cause fatigue that might not go away until a few weeks or months after treatment stops.

7. Taking part - what it involves:

a. Do I have to take part?

Participation in this research is entirely voluntary. A decision to not take part, or to withdraw at any time, will not affect your rights or medical care in any way.

b. How long will my part in this study last?

Three months post radical prostatectomy or EBRT to response of therapy in terms of decline in serum psa. Further follow up will not be included as part of the study.

c. What are the possible benefits in taking part?

Taking part will help in gaining knowledge about the efficacy of radical local therapies, i.e, Radical prostatectomy or EBRT in the management of locally advanced or oligometastatic carcinoma prostate. This may result in improvement of management/outcomes for you/patients like yourself.

d. What are the possible disadvantages and risks of taking part?

There are no major foreseeable disadvantages or risks because of the study. There may be risk of loss of privacy and confidentiality of information collected even though all possible measures will be taken to ensure safe data storage and access.

e. What happens to the information collected from me?

All information collected will be kept strictly confidential and not shared with anyone. Results from the study will be reported as group data and will not identify you in any way.

f. What if I change my mind regarding participation in the study?

You are entitled to change your mind and withdraw at any time during the study without any disadvantage or penalty.

g. Whom do I contact for more information or if I have further questions or concern?

If you want any information or have questions or concerns, you can contact:

Dr. Udit Khurana
Senior Resident (Mch)
Department of Urology, AIIMS Bhopal
8447434114, uditkh0808@gmail.com

It is certified that given translation to vernacular is accurate.

Appendix-3

प्रतिभागी सूचना पत्र

1.**अध्ययन शीर्षक:** रेडिकल लोकल की जैव रासायनिक प्रतिक्रिया (रेडिकल प्रोस्टेटक्टोमी या ईबीआरटी) का मूल्यांकन करने के लिए एक संभावित पर्यवेक्षणीय अध्ययन स्थानीय रूप से उन्नत या ओलिगोमेटास्टेटिक कार्सिनोमा प्रोस्टेट वाले रोगियों में उपचार

2. **अध्ययन अन्वेषक:**

छात्र: डॉ. उदित खुराना, सीनियर रेजिडेंट (एमसीएच), यूरोलॉजी विभाग।

मार्गदर्शक: डॉ कुमार माधवन

सह-मार्गदर्शक: डॉ. देवाशीष कौशल, डॉ. सैकत दास

3. परिचय: हम कट्टरपंथी स्थानीय उपचारों की जैव रासायनिक प्रतिक्रिया का मूल्यांकन करने के लिए एक शोध अध्ययन कर रहे हैं (मौलिक प्रोस्टेटैक्टोमी या ईबीआरटी स्थानीय रूप से उन्नत या ओलिगोमेटास्टेटिक कार्सिनोमा प्रोस्टेट वाले रोगियों में

यह अध्ययन एम्स, भोपाल में किया जा रहा है

4. **अध्ययन का उद्देश्य:** स्थानीय रूप से उन्नत और ऑलिगोमेटास्टेटिक कार्सिनोमा प्रोस्टेट रोगियों में कट्टरपंथी स्थानीय चिकित्सा, यानी ईबीआरटी या रेडिकल प्रोस्टेटक्टोमी की प्रभावकारिता का आकलन करना

स्थानीय रूप से उन्नत और ओलिगोमेटास्टेटिक प्रोस्टेट कैंसर क्या है ?

- स्थानीय रूप से उन्नत प्रोस्टेट कैंसर को T3 से T4 रोग के रूप में परिभाषित किया गया है जो निम्न में से एक या कई को शामिल करने के लिए फैल गया है: प्रोस्टेट कैप्सूल, वीर्य पुटिका, क्षेत्रीय श्रोणि लिम्फ नोड्स, या आसन्न अंग जैसे मूत्राशय, मलाशय, या श्रोणि की दीवार।
- ओलिगोमेटास्टेटिक प्रोस्टेट कैंसर (ओएमपीसी), आमतौर पर इमेजिंग पर पांच या उससे कम मेटास्टैटिक साइटों की उपस्थिति से परिभाषित होता है, स्थानीय और व्यापक मेटास्टैटिक बीमारी के बीच एक संक्रमणकालीन स्थिति का प्रतिनिधित्व करता है और रोग जीव विज्ञान और नैदानिक व्यवहारों के व्यापक स्पेक्ट्रम को शामिल करता है।
- **5.रेडिकल प्रोस्टेटेक्टॉमी क्या है?**
- प्रोस्टेट कैंसर के लिए मुख्य प्रकार की सर्जरी रेडिकल प्रोस्टेटेक्टॉमी है। इस ऑपरेशन में, सर्जन पूरे प्रोस्टेट ग्रंथि को हटा देता है और इसके आसपास के कुछ ऊतक, जिसमें वीर्य पुटिका भी शामिल है।

रेडिकल रेट्रोपुबिक प्रोस्टेटेक्टॉमी

- इस खुले ऑपरेशन के लिए, सर्जन आपके पेट के निचले हिस्से में नाभि से प्यूबिक हड्डी तक एक चीरा (कट) लगाता है।

लेप्रोस्कोपिक रेडिकल प्रोस्टेटैक्टोमी

- लैप्रोस्कोपिक रेडिकल प्रोस्टेटेक्टॉमी (LRP) के लिए, सर्जन प्रोस्टेट को हटाने के लिए पेट की दीवार में कई छोटे चीरों के माध्यम से विशेष लंबे उपकरण सम्मिलित करता है। उपकरणों में से एक के अंत में एक छोटा वीडियो कैमरा होता है, जो सर्जन को शरीर के अंदर देखने देता है।
- लेप्रोस्कोपिक प्रोस्टेटेक्टॉमी के ओपन रैडिकल प्रोस्टेटेक्टॉमी के कुछ फायदे हैं, जिनमें कम रक्त हानि और दर्द, कम अस्पताल में रहना (आमतौर पर एक दिन से अधिक नहीं), तेज रिकवरी समय और कैथेटर को कम समय के लिए मूत्राशय में रहने की आवश्यकता होगी।
- **रेडिकल प्रोस्टेटक्टोमी से जुड़े जोखिम और जटिलताएं**
- ऑपरेशन के दौरान या उसके तुरंत बाद होने वाली समस्याओं में शामिल हो सकते हैं:

  • बेहोशी की प्रतिक्रिया

  • सर्जरी से खून बहना

  • पैरों या फेफड़ों में रक्त के थक्के

  • आस-पास के अंगों को नुकसान

  • शल्य चिकित्सा स्थल पर संक्रमण।

  • शायद ही कभी, सर्जरी के दौरान आंत का हिस्सा घायल हो सकता है, जिससे पेट में संक्रमण हो सकता है और इसे ठीक करने के लिए अधिक सर्जरी की आवश्यकता हो सकती है। खुले दृष्टिकोण की तुलना में लैप्रोस्कोपिक सर्जरी के साथ आंतों में चोट लगना अधिक आम है।

  • यदि लिम्फ नोड्स को हटा दिया जाता है, तो लिम्फ द्रव का एक संग्रह (जिसे लिम्फोसेले कहा जाता है) बन सकता है और इसे निकालने की आवश्यकता हो सकती है।

प्रोस्टेट सर्जरी के साइड इफेक्ट

• मूत्र असंयम (मूत्र को नियंत्रित करने में असमर्थ होना या मूत्र का रिसाव या टपकना। असंयमित होना आपको न केवल शारीरिक रूप से बल्कि भावनात्मक और सामाजिक रूप से भी प्रभावित कर सकता है।

• इरेक्टाइल डिसफंक्शन (नपुंसकता; यौन प्रवेश के लिए इरेक्शन प्राप्त करने या पर्याप्त बनाए रखने में समस्या)

इरेक्शन को प्रोस्टेट के दोनों ओर चलने वाली नसों के 2 छोटे बंडलों द्वारा नियंत्रित किया जाता है। यदि आप सर्जरी से पहले इरेक्शन कर सकते हैं, तो सर्जन प्रोस्टेटैक्टोमी के दौरान इन नसों को घायल नहीं करने का प्रयास करेगा। इसे तंत्रिका-बख्शने वाले दृष्टिकोण के रूप में जाना जाता है। लेकिन अगर कैंसर नसों में या उसके बहुत करीब बढ़ रहा है, तो सर्जन को उन्हें निकालने की आवश्यकता होगी।

सर्जरी के बाद इरेक्शन होने की आपकी क्षमता आपकी उम्र पर निर्भर करती है, ऑपरेशन से पहले इरेक्शन पाने की आपकी क्षमता और क्या नसें कटी हुई हैं। सभी पुरुष इरेक्शन की क्षमता में कुछ कमी की उम्मीद कर सकते हैं, लेकिन आप जितने छोटे हैं, उतनी ही अधिक संभावना है कि आप इस क्षमता को बनाए रखेंगे।

यदि आपकी इरेक्शन की क्षमता सर्जरी के बाद वापस आती है, तो यह अक्सर धीरे-धीरे वापस आती है। वास्तव में, इसमें कुछ महीनों से लेकर 2 साल तक का समय लग सकता है। पहले कुछ महीनों के दौरान, आप संभवत: सहज इरेक्शन नहीं कर पाएंगे, इसलिए आपको दवाओं या अन्य उपचारों का उपयोग करने की आवश्यकता हो सकती है।

स्तंभन दोष के इलाज के लिए कई विकल्प हैं:

• फॉस्फोडिएस्टरेज़-5 (पीडीई5) अवरोधक जैसे कि सिल्डेनाफिल (वियाग्रा), वॉर्डनफिल (लेविट्रा), तडालाफिल (सियालिस), और अवानाफिल (सेंटेंद्र) ऐसी गोलियां हैं जो इरेक्शन में मदद कर सकती हैं। यदि इरेक्शन को नियंत्रित करने वाली दोनों नसें क्षतिग्रस्त या हटा दी गई हों तो ये दवाएं काम नहीं करेंगी।

• एल्प्रोस्टैडिल प्रोस्टाग्लैंडीन ई1 का मानव निर्मित संस्करण है, जो शरीर में स्वाभाविक रूप से बना एक पदार्थ है जो इरेक्शन उत्पन्न कर सकता है। इसे संभोग से 5 से 10 मिनट पहले लिंग के आधार में लगभग दर्द रहित रूप से इंजेक्ट किया जा सकता है या लिंग की नोक में सपोसिटरी के रूप में रखा जा सकता है। इरेक्शन को लम्बा करने के लिए आप खुराक बढ़ा भी सकते हैं।

• निर्वात उपकरण एक ई बनाने के लिए एक अन्य विकल्प हैं इन यांत्रिक पंपों को लिंग के ऊपर रखा जाता है। पंप से हवा को चूसा जाता है, जो लिंग में रक्त खींचकर इरेक्शन पैदा करता है।

• यदि अन्य तरीकों से मदद नहीं मिलती है तो शिश्न प्रत्यारोपण आपकी इरेक्शन की क्षमता को बहाल कर सकता है। उन्हें लिंग के अंदर डालने के लिए ऑपरेशन की जरूरत होती है। कई प्रकार के पेनाइल इम्प्लांट हैं, जिनमें सिलिकॉन रॉड या इन्फ्लेटेबल डिवाइस का उपयोग करना शामिल है।

कामोन्माद में बदलाव: सर्जरी के बाद, कामोन्माद की अनुभूति अभी भी सुखद होनी चाहिए, लेकिन वीर्य का स्खलन नहीं होता है - कामोन्माद "सूखा" होता है।

प्रजनन क्षमता में कमी: रेडिकल प्रोस्टेटेक्टॉमी वास डेफेरेंस को काटती है, जो अंडकोष (जहां शुक्राणु बनते हैं) और मूत्रमार्ग (जिसके माध्यम से शुक्राणु शरीर को छोड़ देते हैं) के बीच के रास्ते हैं। आपके अंडकोष अभी भी शुक्राणु बनाएंगे, लेकिन वे स्खलन के हिस्से के रूप में शरीर को नहीं छोड़ सकते। इसका मतलब यह है कि एक आदमी अब प्राकृतिक तरीके से बच्चे का पिता नहीं बन सकता है। अक्सर, यह कोई समस्या नहीं है, क्योंकि प्रोस्टेट कैंसर वाले पुरुषों की उम्र अधिक होती है। लेकिन अगर यह आपके लिए चिंता का विषय है, तो आप ऑपरेशन से पहले अपने डॉक्टर से अपने शुक्राणु को "बैंकिंग" करने के बारे में पूछ सकते हैं।

लिम्फेडेमा: प्रोस्टेट के आसपास के कई लिम्फ नोड्स को हटाने की यह एक दुर्लभ लेकिन संभावित जटिलता है। लिम्फेडेमा का आमतौर पर भौतिक चिकित्सा के साथ इलाज किया जा सकता है, हालांकि यह पूरी तरह से दूर नहीं हो सकता है।

लिंग की लंबाई में बदलाव: सर्जरी का एक संभावित प्रभाव लिंग की लंबाई में एक छोटी सी कमी है। यह संभवतः मूत्रमार्ग के छोटा होने के कारण होता है जब इसका एक हिस्सा प्रोस्टेट के साथ हटा दिया जाता है।

वंक्षण हर्निया: एक प्रोस्टेटैक्टोमी से भविष्य में वंक्षण (कमर) हर्निया विकसित होने की संभावना बढ़ जाती है।

6.ईबीआरटी क्या है?

ईबीआरटी में, विकिरण के बीम शरीर के बाहर एक मशीन से प्रोस्टेट ग्रंथि पर केंद्रित होते हैं। आप आमतौर पर कम से कम चार सप्ताह के लिए एक आउट पेशेंट केंद्र में सप्ताह में 5 दिन उपचार के लिए जाएंगे। प्रत्येक उपचार एक्स-रे प्राप्त करने जैसा है। एक्स-रे के लिए उपयोग किए जाने वाले विकिरण की तुलना में विकिरण अधिक मजबूत होता है, लेकिन प्रक्रिया आमतौर पर दर्द रहित होती है। प्रत्येक उपचार केवल कुछ मिनटों तक चलता है, हालांकि सेटअप समय - आपको उपचार के लिए जगह में लाने में - अधिक समय लगता है। नई ईबीआरटी तकनीक विकिरण को ट्यूमर पर अधिक सटीक रूप से केंद्रित करती हैं। यह आस-पास के स्वस्थ ऊतकों के विकिरण जोखिम को कम करते हुए ट्यूमर को विकिरण की उच्च खुराक देने की अनुमति देता है।

ईबीआरटी से जुड़े प्रतिकूल प्रभाव?

ईबीआरटी के कुछ दुष्प्रभाव सर्जरी के समान ही हैं, जबकि अन्य अलग हैं।

आंत्र समस्याएं: विकिरण मलाशय को परेशान कर सकता है और विकिरण प्रोक्टाइटिस नामक स्थिति पैदा कर सकता है।

इससे दस्त हो सकते हैं, कभी-कभी मल में रक्त के साथ, और मलाशय का रिसाव हो सकता है। आंत्र समस्याओं को कम करने में मदद करने के लिए, आपको उपचार के दौरान मल त्याग को सीमित करने में मदद करने के लिए विकिरण चिकित्सा के दौरान एक विशेष आहार का पालन करने के लिए कहा जा सकता है। कभी-कभी मलाशय तक पहुंचने वाले विकिरण की मात्रा को कम करने के लिए स्पेसर की तरह कार्य करने के लिए उपचार से पहले मलाशय और प्रोस्टेट के बीच एक गुब्बारे जैसा उपकरण या जेल लगाया जाता है। मूत्र संबंधी समस्याएं: विकिरण मूत्राशय को परेशान कर सकता है और विकिरण सिस्टिटिस नामक स्थिति को जन्म दे सकता है। आपको अधिक बार पेशाब करने की आवश्यकता हो सकती है, पेशाब करते समय जलन हो सकती है, और / या आपके पेशाब में खून आ सकता है।

शायद ही कभी, मूत्राशय से मूत्र को शरीर (मूत्रमार्ग) से बाहर ले जाने वाली ट्यूब बहुत संकीर्ण हो सकती है या बंद भी हो सकती है, जिसे यूरेथ्रल स्ट्रीक्चर के रूप में जाना जाता है। इसे फिर से खोलने के लिए इसे और उपचार की आवश्यकता हो सकती है।

थकान महसूस करना: रेडिएशन थेरेपी से थकान हो सकती है जो उपचार बंद होने के कुछ हफ्तों या महीनों तक दूर नहीं हो सकती है।

7. भाग लेना - इसमें क्या शामिल है:

ए। क्या मुझे भाग लेना है?

इस शोध में भागीदारी पूरी तरह से स्वैच्छिक है। भाग न लेने या किसी भी समय वापस लेने का निर्णय किसी भी तरह से आपके अधिकारों या चिकित्सा देखभाल को प्रभावित नहीं करेगा।

बी। इस अध्ययन में मेरा हिस्सा कितने समय तक चलेगा?

सीरम पीएसए में गिरावट के संदर्भ में चिकित्सा की प्रतिक्रिया के लिए तीन महीने बाद रेडिकल प्रोस्टेटैक्टोमी या ईबीआरटी। आगे की अनुवर्ती कार्रवाई को अध्ययन के भाग के रूप में शामिल नहीं किया जाएगा।

सी। भाग लेने के संभावित लाभ क्या हैं?

भाग लेने से स्थानीय रूप से उन्नत या ओलिगोमेटास्टेटिक कार्सिनोमा प्रोस्टेट के प्रबंधन में कट्टरपंथी स्थानीय उपचारों, यानी रेडिकल प्रोस्टेटैक्टोमी या ईबीआरटी की प्रभावकारिता के बारे में ज्ञान प्राप्त करने में मदद मिलेगी। इससे आपके/आपके जैसे रोगियों के लिए प्रबंधन/परिणामों में सुधार हो सकता है।

डी। भाग लेने के संभावित नुकसान और जोखिम क्या हैं?

अध्ययन की वजह से कोई बड़ा अनुमानित नुकसान या जोखिम नहीं हैं। गोपनीयता और गोपनीयता के नुकसान का जोखिम हो सकता है एकत्र की गई जानकारी के बावजूद सुरक्षित डेटा भंडारण और पहुंच सुनिश्चित करने के लिए सभी संभव उपाय किए जाएंगे।

इ। मुझसे एकत्र की गई जानकारी का क्या होता है?

एकत्र की गई सभी सूचनाओं को कड़ाई से गोपनीय रखा जाएगा और किसी के साथ साझा नहीं किया जाएगा। अध्ययन के परिणाम समूह डेटा के रूप में रिपोर्ट किए जाएंगे और किसी भी तरह से आपकी पहचान नहीं करेंगे।

एफ। यदि मैं अध्ययन में भाग लेने के बारे में अपना विचार बदल दूं तो क्या होगा?

आप अपना विचार बदलने और अध्ययन के दौरान किसी भी समय बिना किसी नुकसान या दंड के वापस लेने के हकदार हैं।

जी। अधिक जानकारी के लिए या यदि मेरे पास कोई और प्रश्न या चिंता है तो मैं किससे संपर्क करूं?

यदि आप कोई जानकारी चाहते हैं या आपके कोई प्रश्न या चिंताएँ हैं, तो आप संपर्क कर सकते हैं:

डॉ. उदित खुराना

वरिष्ठ निवासी (एमसीएच)

यूरोलॉजी विभाग, एम्स भोपाल

8447434114, uditkh0808@gmail.com

यह प्रमाणित किया जाता है कि स्थानीय भाषा में दिया गया अनुवाद सटीक है।

Appendix -4

Participant Informed Consent Form (PICF)]

इस अध्ययन के लिए प्रलिभागी का
पहचान नबरः

Participant Identification Number for this Study:

अनसु धानं का शीर्षकः स्थानीय रूप से उन्नि या ओलिगोमेटास्टेलटक कालसषनोमा प्रोस्टेट के रोलगयों में कट्टरपथीं स्थानीय उपचारों की जैव रासायलनक प्रलिलिया का मलया ू कनं करने के लिए एक सभालविं अविोकन

Title of Project: A Prospective Observational Study to evaluate biochemical response of radical local therapies in patients with locally advanced or oligometastatic carcinoma prostate

शोधकिाष छात्र का नाम: डॉ. डॉ उदित खुराना फोन न: 8447434114

Name of Student Investigator: Dr Udit Khurana Tel No.(s): 8447434114

शोध मागषिशषक का नाम :
डॉ कुमार माधवन

Name of Thesis Guide: Dr Kumar Madhavan

सूचना पत्र संस्करण II दिनांक _____ की जो सामग्री प्रदान की गई थी, वह मेरे द्वारा ध्यान से पढ़ी गई है / मुझे मेरी समझ में आने वाली भाषा में विस्तार से समझाई गई है, और मैंने सामग्री को पूरी तरह से समझ लिया है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है। The contents of the information sheet version II dated_____ that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

अध्ययन की प्रकृति और उद्देश्य और इसके संभावित जोखिम/लाभ और अध्ययन की अपेक्षित अवधि, और अध्ययन के अन्य प्रासंगिक विवरण मुझे विस्तार से बताए गए हैं। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मैं किसी भी समय, बिना कोई कारण बताए, अपनी चिकित्सा देखभाल या कानूनी अधिकार को प्रभावित किए बिना इसे वापस लेने के लिए स्वतंत्र हूं। The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

मैं इस शोध में मेरी भागीदारी से मेरे बारे में एकत्र की गई जानकारी और मेरे किसी भी मेडिकल नोट्स के अनुभागों को एम्स के जिम्मेदार व्यक्तियों द्वारा देखा जा सकता है। मैं इन व्यक्तियों को मेरे रिकॉर्ड तक पहुंच की अनुमति देता हूं। I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for this individual to have access to my records.

यदि प्रतिभागी बच्चा है, तो उसकी मौखिक लिखित सहमति प्राप्त कर ली गई है।। If participants is child, his/her verbal of written assent has been obtained.

मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं /I agree to take part in the above study.

(हस्ताक्षर/बाएं अंगूठे का निशान) (Signature/Left Thumb Impression) लिनाक:

/Date……स्थान/Place

……..... प्रलिभागी का नाम/Name of the participant…….....

30

लपिा/पलि/पत्नी का नाम /Son/Daughter/Spouse of……. पूरा डाक पता /Complete Postal Address ……....

अगर अलशलक्षि हों /

If illiterate.

सूचना पत्र को प्रतिभागी को पढ़ा और समझाया गया है और प्रश्न पूछने का अवसर दिया गया है। मैं पुष्टि करता हूं कि व्यक्ति ने स्वतंत्र रूप से सहमति दी है।

The information sheet has been read and explained to the participant and given the opportunity to ask questions. I confirm that the individual has given consent freely.

कानूनी रूप से स्वीकार्य प्रतिनिधि या निष्पक्ष गवाह के हस्ताक्षर।

Signature of Legally acceptable representative or impartial witness.

लिनाक /Date एिएआर या लनष्पक्ष गवाह का नाम /

Name of LAR or impartial witness.

पता / Address: -

प्रमाणित किया जाता है कि उपरोक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।This is to certify that the above consent has been obtained in my presence.

छात्र अन्वेषक के हस्ताक्षर दिनांक …… स्थान ……Signature of the student Investigator Date ……Place ……

Appendix 5

Master chart

Age (Y	Age	PSA (n	PSA (ng/	PIRADS sco	ISUP	Management	T Stag	T Stag	N Stag	N Stag	M Stag	Numbe	Clavien Di	LVI	PNI	Margins	ADT	Comments
66	60-69 Years	50	0.15	PIRADS 5	Grade 4	Radical Prostatectomy	T3b	T3b	N0	N0	M0	0	Grade 1	No	Yes	Negative	No	
67	60-69 Years	142	0.07	PIRADS 5	Grade 3	Radical Prostatectomy	T3a	T3b	N0	N1	M0	0	Grade 2	No	Yes	Negative	No	
49	40-49 Years	51	0.01	PIRADS 5	Grade 3	Radical Prostatectomy	T3b	T3b	N0	N0	M0	0	Grade 3	No	No	Negative	No	
71	70-79 Years	34	0.04		Grade 3	Radical Prostatectomy	T2	T2	N0	N0	M0	0	Grade 1	No	Yes	Negative	No	
45	40-49 Years	71	0.5		Grade 4	Radical Prostatectomy	T3a	T3a	N0	N0	M0	0	Grade 2	No	Yes	Positive	No	
66	60-69 Years	39	0.15	PIRADS 3	Grade 3	Radical Prostatectomy	T3a	T3b	N0	N0	M0	0	Grade 1	No	Yes	Negative	No	
72	70-79 Years	14	0.03	PIRADS 5	Grade 5	Radical Prostatectomy	T2	T2	N0	N1	M0	0	Grade 3	Yes	Yes	Negative	No	
67	60-69 Years	23	0.79	PIRADS 5	Grade 4	Radical Prostatectomy	T3b	T3b	N1	N1	M0	0	Grade 1	No	Yes	Negative	Yes	Bladder Neck Sparing
66	60-69 Years	35	5.258	PIRADS 5	Grade 5	Radical Prostatectomy	T3a	T3b	N0	N1	M0	0	Grade 3	Yes	Yes	Positive	No	Lost To Follow Up
62	60-69 Years	27	0.011	PIRADS 5	Grade 2	Radical Prostatectomy	T2	T2	N0	N0	M1b	1	Grade 1	No	No	Negative	No	
57	50-59 Years	29	0.017	PIRADS 5	Grade 4	Radical Prostatectomy	T3b	T3b	N1	N1	M0	0	Grade 2	No	Yes	Negative	No	
54	50-59 Years	79	0.079	PIRADS 5	Grade 3	Radical Prostatectomy	T3b	T3b	N1	N1	M0	0	Grade 2	No	Yes	Negative	Yes	Bladder Neck Sparing
58	50-59 Years	14	0.002	PIRADS 5	Grade 2	Radical Prostatectomy	T3a	T3b	N0	N0	M1b	1	Grade 1	No	Yes	Negative	No	
61	60-69 Years	14	0.008	PIRADS 3	Grade 4	Radical Prostatectomy	T2	T2	N0	N0	M1b	1	Grade 1	No	Yes	Negative	No	
50	50-59 Years	100	0.373	PIRADS 5	Grade 5	Radical Prostatectomy	T4	T3b	N1	N1	M0	0	Grade 1	No	Yes	Negative	Yes	
65	60-69 Years	45	0.05	PIRADS 5	Grade 2	Radical Prostatectomy	T3a	T2	N0	N0	M0	0	Grade 1	No	Yes	Positive	No	
73	70-79 Years	9	2.2	PIRADS 5	Grade 5	Radical Prostatectomy	T2	T3a	N0	N0	M1b	1	Grade 1	No	Yes	Negative	No	
76	70-79 Years	6	0.124	PIRADS 4	Grade 3	Radical Prostatectomy	T3a	T3a	N0	N0	M1b	4	Grade 1	No	No	Negative	No	
63	60-69 Years	27	0.004	PIRADS 4	Grade 1	Radical Prostatectomy	T2	T2	N0	N0	M1b	1	Grade 1	No	No	Negative	No	
65	60-69 Years	21	1.04	PIRADS 4	Grade 4	Radical Prostatectomy	T2	T3b	N0	N0	M0	0	Grade 2	No	Yes	Positive	No	
64	60-69 Years	15	0.04	PIRADS 4	Grade 1	Radical Prostatectomy	T2	T2	N0	N0	M1b	1	Grade 1	No	No	Negative	No	
63	60-69 Years	28	0.08	PIRADS 5	Grade 1	Radical Prostatectomy	T3a	T2	N0	N0	M0	0	Grade 1	No	Yes	Negative	No	
64	60-69 Years	30	0.144	PIRADS 5	Grade 5	Radiotherapy	T3b	T3b	N0	N0	M0	0		No	Yes			
73	70-79 Years	24	0.152	PIRADS 5	Grade 1	Radiotherapy	T3b	T3b	N1	N1	M0	0		No	No			
74	70-79 Years	61	0.029	PIRADS 5	Grade 3	Radiotherapy	T3b	T3b	N1	N1	M1b	1		No	Yes			
53	50-59 Years	203	0.017	PIRADS 5	Grade 4	Radiotherapy	T3b	T3b	N1	N1	M0	0		Yes	Yes			
68	60-69 Years	37	0.004	PIRADS 5	Grade 5	Radiotherapy	***T4***	***T4***	N1	N1	M0	0		No	Yes			
65	60-69 Years	20	0.008	PIRADS 5	Grade 3	Radiotherapy	T3b	T3b	N0	N0	M0	0		No	Yes			
70	70-79 Years	18	0.247	PIRADS 5	Grade 3	Radiotherapy	T3b	T3b	N0	N0	M1b	2		No	Yes			
74	70-79 Years	84	0.23	PIRADS 5	Grade 5	Radiotherapy	***T4***	***T4***	N1	N1	M1b	***1***		No	Yes			